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ABSTRACT

EFFECT OF 3D PRINTED TABLET SHAPE ON DRUG RELEASE PROFILE

by
Christina Gedeon

There is a growing interest in utilizing additive manufacturing (AM) as a manufacturing tool to develop oral tablets for personalized medicine. This ultimate goal in mind, this study explores the feasibility of extrusion-based fused deposition modeling (FDM) to 3D print oral tablets with tunable design to control drug release profile. Tablets are printed using poly(vinyl alcohol) (PVA) loaded with model drugs: acetaminophen and caffeine. Hot melt extrusion (HME) is used to fabricate PVA filaments loaded with acetaminophen and caffeine. These filaments are used to fabricate a range of tablets with varying designs to prepare immediate and delayed release tablets. Thermal characterization combined with rheology is used to determine the processing (extrusion) and printing temperature, and to confirm that none of the ingredients are degraded throughout these processes. Both of the model drugs remained amorphous post-extrusion and post-printing. Dissolution tests show that 80% of the acetaminophen is released within 30 minutes for the immediate release tablets. For the delayed release studies, the lag time of 30, 90 and 120 minutes are observed for 0.5, 1 and 1.5 mm coating of PVA, respectively. Our results show that FDM is a promising way for personalized medicine where the release can be controlled by changing the tablet design.

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by
Christina Gedeon

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APPROVAL PAGE

EFFECT OF 3D PRINTED TABLET SHAPE ON DRUG RELEASE PROFILE

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This thesis is dedicated to my beloved

Parents, Michel Gedeon and Seta Kutnerian

Brother, Antoine Gedeon

and Friends.

Who supported me all along the way

هذا العمل مكرس إلى أحبائي

أهلي ميشال جدعون وساتا كوتنريان

أخي أنطوان جدعون

واصدقائي

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CHAPTER 1

LITERATURE REVIEW

1.1 Introduction

Three-dimensional printing is an additive manufacturing technique based on forming a 3D model layer by layer. The idea of 3D printing started in the 1970s by Pierre Ciraud who described the method of using a powdered material, solidifying it using a high energy beam and building the model layer by layer. In the 1980s, Ross Housholder introduced the idea of sand binding and Carl Deckard introduced selective laser sintering. The first commercial technology is stereolithography (SLA) and is created by Chuck Hull [1]. Currently, 3D printing is gaining a lot of attention and it is used in diverse fields such as aerospace, automotive, medical and architecture. In these industries, it can be used for rapid prototyping and research. In the medical industry, 3D printing is used for bioprinting, organ printing, body part printing, tissue engineering and medical devices printing. Although it has pros and cons, 3D printing is introduced in the pharmaceutical industry to print tablets, or printlets [2].

In the pharmaceutical industry, most drugs are delivered orally as oral solid dosages. Table 1.1 represents the advantages and disadvantages of the production and administration of tablets. Introducing additive manufacturing in this industry can lead to a shift in the design, manufacture and usage of drugs. The production will move from traditional mass manufactured tablets to customized or personalized tablets. Drug development is a long and expensive multistage process and 3D printing can improve it and reshape it [3]. Using 3D printing in the early drug discovery steps and the

manufacturing steps reduces the time and cost by producing small batches of drugs to be tested. As shown in Figure 1.1. Compared to the conventional method, many steps are eliminated such as wet granulation, dry granulation and tablet compression [4]. For the production stage, 3D printing makes it is possible to manufacture an immediate release and targeted release delivery system by modifying shape and density of the design. 3D printing makes it possible to print shapes that cannot be achieved by molding [5]. All these potentials show that 3D printing is a promising technology that can lead to a personalized and customized oral solid dosage based on each patients' needs.

Table 1.1 :Advantages and Disadvantages of Oral Solid Dosages

Advantages	Easy for the patient to take and carry
	High chemical and microbial stability
	Easy to mask taste and odor
	Taking fraction of a dose is possible
	Possible to formulate controlled release profiles
	Easy packaging, shipping and dispensing
	Great dose precision
Disadvantages	Swallowing problems
	Some APIs are tricky to formulate
	Long procedure to produce
	Coating may be required

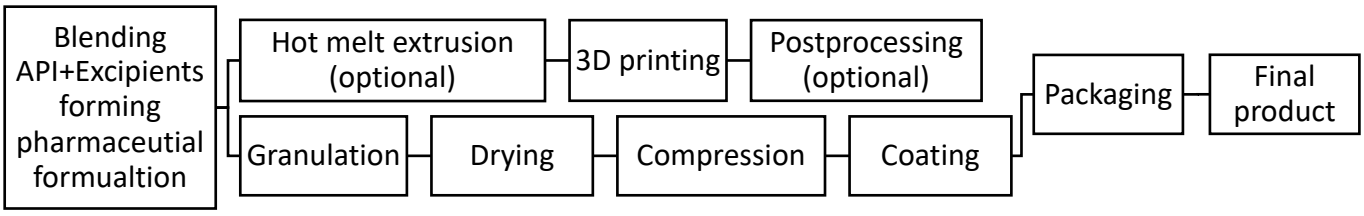


Figure 1.1 The comparison between the conventional method and 3D printing method to produce oral solid dosages.

Drug delivery is defined by Goole et al (2016) as the approaches, systems, technologies and formulations for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect [6]. Drug delivery is affected by many criteria like gender, age, race and patient condition. It is important to highlight the diversity among human, different drug formulations are required for different groups of people. Age is a key point for drug delivery. Additional considerations are required when formulating medicines for elders and kids. Physiological and cognitive responses differ due to developing or deteriorating conditions of the body [7]. While taste and smell are important factors for pediatric medicine, the main challenge is safe swallowing. The ability to swallow oral solid dosages depends on the age of the patient and the size of the tablet. Both elders and kids may have swallowing difficulties or dysphagia. Shiele et al (2013) discusses the difficulties related to swallowing, including causes, prevalence and the relationship with the dosage form [8]. Also, older adults are usually on multiple medications, and caregivers may be involved. Directions about multiple medicines may be complicated for both the caregiver and the elder. This diversity highlights the importance of production of personalized tablets with specific regimen and release and with multiple APIs [9].

The goal behind using additive manufacturing is to reduce cost and time and manufacture a highly adjustable and accurate dose that can be easily prepared or controlled by pharmacists. Controlled release tablets are important, and the objective is to get an effective therapy avoiding overdosing and under dosing while maintaining the drug concentration within the therapeutic window. Controlled release is typically achieved by coating. With the usage of 3D printers, it is possible to alter the release profile just by modifying operating conditions like infill density or by changing the polymer used. Consequently, this will reduce the production time and cost. Besides time and money, since multiple APIs can be incorporated within one tablet, personalized medicine will result in fewer administration, leading to higher patient compliance. It is also achievable to produce multidrug tablets based on the patient needs and the printer used. In addition, most 3D printers are not complex and are simple to use if all materials such as filaments and mixtures are provided. Healthcare providers in pharmacies and hospitals can be trained to use this new technology.

Furthermore, due to the development in technologies used for drug delivery, pharmaceutical companies started focusing on 3D printing for manufacturing tablets. In 2016, the US food and drug administration (FDA) approved the first oral solid dosage manufactured using a 3D printer by the company Aprecia Pharmaceuticals. The idea is developed at the Massachusetts Institute of Technology (MIT) in the 1980s. The tablet is printed by spreading drug in the powder form and depositing a liquid on it layer by layer. The number of layers depends on the dosage to be achieved which is 1000 mg in their formulation [10]. The approved drug is marketed as Spirtam and it is an anticonvulsant levetiracetam for treating adults and children with epilepsy [11]. The release profile is immediate, and the pill disintegrates immediately when administered with water due to its high porosity.

1.2 Additive Manufacturing Technologies

Additive manufacturing describes processes building 3D models by extruding layer by layer of a certain material that depends on the technology. Additive manufacturing methods used in the pharmaceutical industry can be divided into 3 categories as shown in Figure 1.2.

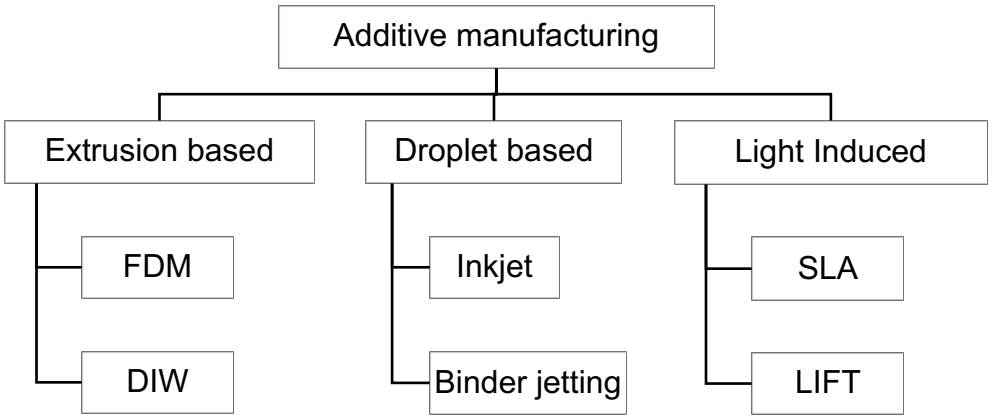


Figure 1.2 Categories of additive manufacturing methods.

1.2.1 Extrusion-based Technologies

Extrusion based technologies are one of the most popular methods used for 3D printing. Printing is done using heat or pressure to extrude the material on a platform layer by layer. FDM and DIW are examples of this technology.

- Fused deposition modeling (FDM)

Fused deposition modeling is a widely used 3D printing method; it is based on a layer by layer extrusion of thermoplastic filaments such as polylactic acid (PLA), acrylonitrile butadiene styrene (ABS) or polyvinyl alcohol (PVA). First of all, the 3D model is designed using a computer aided design software. The model is saved as a stereolithography file (.stl) then sliced in the z-direction using the slicer program associated with the printer to be used. A spool of a filament is loaded in the printer

where the gears rotate to push the filament into the heating zone. The filament melts and is deposited through the nozzle on the printing platform where it cools. In some cases, a fan can be used to accelerate the cooling process. After printing, postprocessing is optional such as coating. To control the quality of the print, many printing setups can be modified such as printing temperature, layer height, printing speed and infill density. The advantages of using FDM are the simplicity of the technology, the high printing rate and the low cost.

- Direct ink writing (DIW)

Similar to fused deposition modeling, direct ink writing is also based on depositing materials and layer by layer printing. However, the main difference is that many materials can be used to print including liquids, melts (from pellets) or gels (hydrogels) whereas FDM is limited to filaments. A 3D model saved as stl file is also required, then it is sliced in the z-direction. Syringes or cartridges are filled with the material and air pressure is applied to push the material to be deposited through the nozzle on the printing plate. Heating of the material is optional; some material can be printed at room temperature and others require heating and melting to be able to print. Main uses of 3D printing are for bone regeneration, cartilage regeneration, soft tissue bio fabrication and drug release.

1.2.2 Droplet-based Technologies

This method is done using droplets of a material, it can be a resin that is cured or a binder to bind powder particles. Two technologies are discussed: Inkjet and binder jetting.

- Inkjet

Inkjet 3D printing is an additive manufacturing process based on dispensing droplets of photosensitive material. These materials are thermoset and solidify when cured under

UV light. The process starts with heating the resin to get the viscosity required for printing. Then, the nozzle moves over the printing platforms depositing droplets of the resin by applying pressure. The layer of jetted droplets is cured by UV forming a solid layer. The platform moves down between layers and the process is repeated to form the 3D model.

- Binder jetting

Binder jetting is an important additive manufacturing method in the pharmaceutical industry. The first FDA approved 3D printed drug is manufactured using binder jetting. In this method, the building platform is coated by a blade with a layer of powder. Then, droplets of a binding agents are deposited binding powder particles and forming a solid. The binder acts like a bridge between the powder particles. Between layers, the platform moves down, and the platform is recoated with the powder. Usually, postprocessing is required after the print is ready. Sintering is done by heating to reduce the porosity of the final 3D object. The quality of the print depends on the properties of the powder and liquid binder.

1.2.3 Vat-polymerization

3D printing using VAT polymerization is done by constructing layers with a liquid photopolymer and curing it using UV light forming a solid. Examples of VAT polymerization technologies are SLA and SLS.

- Stereolithography Apparatus (SLA)

SLA is based on solidification of resins by curing it layer by layer with UV light. In SLA, the building platform starting position is at a distance of one-layer height of the liquid photopolymer. The layer is exposed to UV where the monomer carbon chains are activated forming strong unbreakable bonds resulting in the solidification of the resin. After the layer is done, the printing platform moves, and it is recoated with the

resin. The process is repeated to make the 3D model. Post printing curing may be required in some cases. There are two types of SLA printers, one where the light source is below the resin tank and the building platform moves up and another one where it is above the resin tank and the building platform moves down. Materials usually used in this method are thermoset polymers that irreversibly harden when cured.

- Selective laser sintering (SLS)

SLS is an additive manufacturing method where particles are fused together by sintering polymer powder using a laser. It is usually used for plastic, metallic and ceramic objects. The process starts with melting the polymer powder just below the melting temperature. Then a blade spreads a thin layer on the building platform. The laser selectively sinters the powder and the particles are fused together forming a solid layer. Next, the blade recoats the platform with another thin layer and the process is repeated until all the layers are printed forming the final 3D model. The main advantage of SLS is that the non-sintered powder acts like a support, therefore supports are not required when printing. The drawback when using SLS is the limited choice of powder polymer that can be sintered using laser.

1.3 Materials

1.3.1 Polymers

Polymers are the most versatile category of biomaterials. The suitable polymer selected should deliver the API without interacting with it in the appropriate site of action, should not have side effects, and should be printable using the selected printer. The selection of the polymer is based on the printing technology selected and the release profile aimed. Moreover, the polymer used can be in many forms including filaments, powders, pastes, solution or colloids. There are many materials that can be used to print tablets including methacrylic polymers, cellulose based polymers, polyvinyl alcohol, and polycaprolactone.

- Cellulose based polymers

They have cellulose as a precursor. This polymer is a potential substitute to petroleum-based polymers. However, due to very strong hydrogen bonding in pure cellulose, it degrades before melting, therefore it cannot be used alone. The solution for this problem is to use cellulose in a mixture with other materials [12]. Paggi et al (2018) tested mechanical properties of 3D printed tablets using a mixture of cellulose acetate and corn starch and proved that this mixture is biodegradable and biocompatible and feasible to extrude by HME and print using the FDM [13]. An example of a cellulose based polymer is Hydroxypropyl cellulose (HPC), it is a cellulose ether. HPC is hydrophobic, soluble in water and polar organic solvents. Its use depends on its molecular weight. Having a low molecular weight it acts as a binder, and having high molecular weight it acts as a controlled release matrix [14].

- Polyvinyl alcohol (PVA)

It is a colorless, tasteless, and odorless thermoplastic. It is soluble in water and non-soluble in organic solvents. It is also considered safe by the FDA since it is inert, stable, and it is proven that it does not have adverse effect when administered in the body. It is also included in the FDA inactive ingredients database [15]. PVA is produced by partial or full hydrolysis of polyvinyl acetate by removal of the acetate group. The melting point of PVA depends on the hydrolysis degree and it ranges from 180 to 220 °C. The higher the degree of hydrolysis, the lower the molecular weight and the higher the solubility in water [16]. Because of its biocompatibility, non-toxicity, water solubility and good mechanical and swelling properties, PVA has gained attention as an excipient to oral solid dosages [17]. In the body, PVA is poorly absorbed in the gastrointestinal tract and is easily eliminated from the body. However, it is this behavior that varies for different PVA molecular weight. PVA should not be kept at high temperature for a long time because it will degrade, emit carbon and become toxic. It should be stored tightly sealed container in a cool, dry place [15]. PVA is incompatible with a compound with secondary hydroxy group because it may undergo esterification. Moreover, PVA is available as commercial filaments. Besides the production of oral solid dosages, it is widely used in the pharmaceutical industry to make transdermal patches [18, 19], topical delivery systems [4, 20], and mucoadhesive and viscosity enhancer for ocular delivery [21].

- Methacrylic polymers or Eudragit

It was first introduced in the 1950s for enteric coating. It is prepared by polymerization of acrylic and methacrylic acids and their esters [22]. This polymer can achieve a flexible and targeted release profile. It can be an immediate release or a sustained release. For example, Eudragit S and L can withstand the acidic media of the stomach and the drug will be released in the intestine. In addition, Eudragit is available in

different degrees of solubility. Patra et Al (2017) explained different grades of Eudragit in details [23]. In the body, the release of the API depends on the degree on Eudragit used, its solubility depends on the pH. The application of using Eudragit is to target a certain delivery such as ophthalmic [24, 25], buccal or sublingual [26], enteric [27], oral [28, 29], colon [30], vaginal [31], and transdermal [32].

- Polycaprolactone (PCL)

It is a semi crystalline hydrophobic aliphatic polyesters can be synthesized via polycondensation of hydroxycarboxylic acids and catalytic ring-opening polymerization of lactones [15]. PCL is not soluble in neither water nor alcohol. It is degraded by bacteria in fungi in the environment, however, the body lacks the proper enzymes to degrade it [16]. In addition, the degradation of PCL is longer than other polymers, therefore it can be used for long time degradation devices [16]. For regulations, PCL is generally recognized as safe (GRAS) by the FDA [15]. In the pharmaceutical industry, PCL is used in tissue engineering [33, 34], wound dressing [35], and drug delivery system [36-38].

- Polyvinylpyrrolidone (PVP)

It is a polymer synthesized by free radical polymerization from its monomer N-vinylpyrrolidone. It is hygroscopic, soluble in water and polar solvents but insoluble in hydrocarbons. Solubility differs with different degrees of polymerization. Its molecular weight ranges from 2500 and 2900000 daltons [39]. PVP is employed in 3D printing technologies to form tablets such as FDM, DIW and binder jetting. PVP acts as a coating agent or a binder for wet granulation due to its good wetting properties and ability to form films. In addition, it is widely used for topical delivery by mixing it with iodine forming a complex used for solutions and ointments. It is also added in formulations for parenteral and ophthalmic administrations [40]. For regulations, PVP

is physiologically inert and considered safe to use in pharmaceuticals. Its storage is simple, and it can be kept under ordinary conditions without undergoing degradation or decomposition. It is only affected if the temperature reaches 150°C since it darkens and becomes less soluble [15]. Being hygroscopic, it is important to prevent moisture absorption too.

In addition to the polymers listed above, multiple polymers can be mixed to optimize the printability of a pharmaceutical formulations. Ilyés et al (2019) tested the printability of different polymeric blends. Kollidon SR (8:2 of PVA:PVP), Affinosol 15LV (modified hydroxypropyl methylcellulose with lower glass transition) and other mixtures are extruded, printed and compared [41]. Fina et al used Kallicoat IR (75% PVA and 25% polyethylene glycol) as a copolymer to print paracetamol tablets using selective laser sintering [42].

1.3.2 Additives

Since a convenient oral solid dosage cannot be achieved with the active ingredient alone, other ingredients are added to pharmaceutical formulations. Additives or excipients are substances added to the formulations without having any therapeutic effect. They can either be natural or synthetic [43]. Additives play a vital role in the design and performance when manufacturing oral solid dosages. They improve the processing during manufacturing and they enhance stability, effectiveness and patient compliance [44, 45]. When selecting an excipient, many factors should be taken into consideration. A convenient excipient is be inert, inactive, physically and chemically stable throughout the shelf life, compatible with other additives and APIs and complies with regulatory bodies requirements. Despite being inactive, excipients are very important and affect the pharmaceutical performance and release profile. Regulatory bodies monitor excipients and have a list of approved additives to be used in

pharmaceutical manufacturing. When making tablets, excipients such as binder, lubricant, filler, disintegrant, coating agent, stabilizer, emulsifier, coating agent and viscosity enhancer are added to pharmaceutical formulations [46]. Not all listed excipients are included in formulations, only the ones needed for an easier and smoother process.

- Plasticizers

They are added to polymers or polymeric blends to improve mechanical and thermal properties. They are inert, organic, and non-volatile compounds that have low molecular weight. Plasticization can be done by two different methods: Internal plasticization and external plasticization. Internal plasticization is done by chemical modification to increase flexibility and external plasticization is done by adding a plasticizer without altering the chemistry of the polymer [47]. Plasticizers are classified into two categories. Primary plasticizers are added to lower the glass transition which is the temperature at which the polymer goes from a glass phase to a rubbery phase. They also improve flexibility, processability, distensibility, and stretch ability. On the other hand, secondary plasticizers are used in addition to the primary one to enhance its effect [47, 48]. Nevertheless, the main disadvantage of the plasticizer is that it may migrate from the bulk to the surface. The lower the molecular weight and the more linear the structure lead to higher extraction and migration. In addition, for nature and health related issues may be associated with the usage of plasticizers. Bialecka et Al discusses the environmental and health issues related to different types of plasticizers [49]. Moreover, since plasticizers are inert, their packaging and storage is simple and safe, however they should not be stored at high temperature to avoid deterioration. The mostly used plasticizer in the pharmaceutical industry is triethyl citrate (TEC) [50, 51].

- Lubricant

They are added in small quantities when mixing dry powders before printing or extruding filaments. The goal behind using lubricants is to prevent ingredients from clumping together, improve the powder flow and reduce friction. Pharmaceutical lubricants are divided in three categories: glidants, ant-adherent and die wall lubricant [52]. Anti-adherent excipients reduce the adhesion properties of a tablet and prevents the mixture from sticking to equipment and machines including hot melt extrusion and mixer by reducing the friction between the surface of the equipment and the mixture. Glidants improve flowability of powder blends by reducing interparticle friction. Poor flow can lead to insufficient mixing and poor content uniformity. Die wall lubricants reduces friction between the surface of the tablet and the die wall. There are many lubrication mechanisms hydrodynamic, elastohydrodynamic, mixed and boundary lubrication [53]. Lubricants are required for successful manufacturing; it is used for better quality and smoother operations. A good lubricant should have low shear strength, should not be toxic, and should not be affected by process variables [54]. Lubricants can be either hydrophilic or hydrophobic. However, hydrophobic ones are more frequently used because they are effective at low concentrations. The most commonly used lubricants in the pharmaceutical industry are talc, silica, magnesium stearate, or stearic acid.

- Disintegrants

They are added to pharmaceutical formulations to ensure fast disintegration and dissolution. The role of disintegrants is to accelerate drug release. They are classified in two types: superdisintegrants and normal disintegrants. The difference between these two is that superdisintegrant is added in lower concentrations but results in better disintegration, the tablet swells up faster and has better powder compression properties compared to normal disintegrants [52]. To initiate disintegration, it first promotes

moisture penetration into the tablet matrix. It ensures the fragmentation of the dosage form into smaller particles upon ingestion to allow immediate release and absorption. In general, disintegrants are hydrophobic and insoluble in both water and gastrointestinal juices. There are many mechanisms proposed and associated with disintegrants [55]. Most commonly it is explained by the process of swelling where the components are pushed apart initiating the breakup of the tablet matrix. The swelling ability depends on the chemical structure, the degree of cross linking and the porosity of the matrix. Furthermore, the performance of the disintegrants depends on many factors including the particle size, the moisture content and the method of incorporation within the formulation. Desai et al (2014) tested rapidly disintegrating tablets incorporating APIs with different solubilities, while investigating the effect of different disintegrants on the dissolution and tablet hardness [56]. The most frequently used disintegrants for pharmaceutical formulations are starch and its derivatives and cellulose and its derivatives. Sadia et al (2018) tested different disintegrants to find the one resulting in the fastest drug release [50].

- Binding agents

They are added to pharmaceutical formulations to increase cohesion in the powder mixture leading to better hardness and friability. They are either added in solution or in dry powder form. There are three types of binders: natural, synthetic and sugars [57]. Polymeric binding agents are hydrophilic, and they increase wettability of poorly soluble drugs resulting in improved dissolution. Many factors affect the particle size including the binder concentration, viscosity, quantity and addition method [52].

- Fillers

They are added to formulations where the API is present in small quantities and is not enough to form a tablet. They increase the volume of the mixture and therefore it is

possible to get an average-sized pill. Fillers usually have a weak binding capacity; thus, binders and fillers are used together. Sadia et al (2016) tested the nature of tri-calcium phosphate (TCP) as a filler and different polymer: filler ratio to print tablets using eudragit as a polymer.

1.3.3 Drugs

The choice of drug to be used in the 3D printed tablet is usually a model drug. The drug chosen depends on the printer used. If printing is done at high temperature using FDM, the drug used should be thermally stable to avoid degradation. If printing is done using SLA or LIFT, studies should be done to make sure the drug is not affected by UV.

Furthermore, the drug selected depends also on the targeted release. When the goal is to modify the immediate release to get extended release, paracetamol or caffeine is used. Paracetamol is a drug that alleviates mild to moderate pain and Caffeine is a stimulant to reduce fatigue. These drugs are usually produced as immediate release oral solid dosages. Goyanes et al (2017) used Paracetamol as the model drug because it is common, inexpensive, highly soluble and highly permeable and the study is based on extending the release [58]. Sadia et al (2018) used Hydrochlorothiazide as a drug with low permeability and low solubility because their goal is to accelerate drug release by maintaining good bioavailability [50]. Pietrzak et al (2015) selected Theophylline because it is a thermostable model drug and it will not be affected by heating while extruding [51]. Table 1.2 summarizes the drugs employed in researched and their effect on the body.

Table 1.2 Different Drugs Used to Research 3D Printing in the Literature and Their Action on the Body

Drug	Effect on the body	Reference
4-ASA (4-Aminosalicylic acid)	Antibiotic primarily used to treat tuberculosis	[59]
5-ASA (5-aminosalicylic acid or Mesalamine)	Anti-inflammatory	[60]
Aripiprazole	Antipsychotic	[61]
Aspirin	Reduce risk of blood clotting and reduce the risk of heart attacks and strokes	[62]
Atenolol	Used to treat hypertension and prevent heart attack	[62]
Budesonide	Treats inflammatory bowel disease	[63]
Caffeine	Stimulant to reduce fatigue	[64]
Captopril	Lowers blood pressure (for hypertension)	[65]
Deflazacort	Immunosuppressant and anti-inflammatory	[66]
Domperidone	treats gastroparesis and other conditions causing chronic nausea and vomiting	[67]
Hydrochlorothiazide	Prevent absorption of too much salt and treat oedema	[62]
Paracetamol/Acetaminophen	Analgesic and Antipyretic	[4]
Pravastatin	Reduces blood cholesterol and triglyceride in hyperlipidemic patients	[62]
Prednisolone	Anti-inflammatory	[68]
Ramipril	Angiotensin (increase blood pressure)	[62]
Theophylline	Bronchodilator	[69]

1.4 Tablet Printing Using Different Technologies

Many technologies are researched to produce tablets of different release profiles and different shapes (Table 1.3). Not all 3D printing technologies can be used in the pharmaceutical industry. Some methods are well established while others are still at the development stage. The selection of technology depends on the components of the pharmaceutical formulation. So far, the technologies tested are FDM, DIW, SLS, SLA and binder jetting. Figure 1.3 represents the processes using these technologies to print tablets.

1.4.1 Using FDM Printers

To print a tablet using an FDM printer, a filament infused with drug is required. There are two method to get the filaments; the first method consists of soaking the filament in a liquid suspension, the drug will diffuse in the polymer. Drying is mandatory after soaking to be able to use the filament in the printer. The amount of drug is limited using this method to form filaments. Furthermore, soaking and drying can be time consuming. The drug can also be incorporated post printing, where a tablet is printed using a commercial filament, then it is soaked in a liquid suspension. The second method consists of using hot melt extrusion (HME). All APIs and excipients are weighed precisely and mixed well to form a homogeneous powder mixture. The mixture is then fed to the hot melt extruder where it is subjected to heat and pressure where it melts. Both screws in the extruder rotate and push the material out of the nozzle forming a filament. Chokshi et al (2004) explained in details the hot melt extrusion process [70]. Hot melt extrusion is an important process that can be widely used for drug delivery [71, 72]. According to Zhang et al (2017), HME is the preferred method to make solid filament with better drug dispersion and with good mechanical properties. It can also be used to make enteric capsules, Mehuys et al (2005) formed hollow cylinders using

hot melt extrusion, filled them with a model drug and encapsulated them [73]. When making filaments, it is important to take into consideration the restrictions related to the used printer. To be able to load the filament, it should have a minimum of 1.75 mm. The diameter should also be consistent for uniform printing. In addition, it should not be too brittle to avoid filament breaking during printing. Excipients such as lubricant and plasticizer play a major role in extruding the filament. Using HME, it is possible to get a high amount of drug with a high dose flexibility [74]. Once the filament is ready it can be used in the FDM printer. It is loaded in the printer and the tablet is printed on the platform as explained previously. When all tablets are printed and ready, in-vivo and in-vitro studies are done.

Researchers used drug infused polyvinyl alcohol (PVA) and printed tablets to study the drug release of tablets with different geometries [75] and with different loading [76]. Others used drug loaded Eudragit as an excipient and studied the drug release of different designs of channels for the tablet [50], different printing resolution and different drug dosages [51].

Oral solid dosages printed using FDM can have an immediate release profile or a controlled release profile. The advantage of this method is that it is fast, effective and easy to use. In addition, it is possible to print complex models that cannot be achieved using powder compaction to control the release. In addition, coating is not required to achieve delayed release, it can be achieved by changing the polymer used. However, FDM cannot be used for heat sensitive API or excipients because of degradation. Okwuosa et al (2016) tested a lower temperature to print tablets by FDM using PVP as the polymer [77].

1.4.2 Using Direct Ink Writing or Bio-plotter

DIW is recently introduced in the pharmaceutical and the biomedical industry. First, excipients and API are mixed resulting in a paste like mixture. The printer cartridge is filled with the paste and tablets are printed. The oral solid dosage release profile is then studied with dissolution test and HPLC. In some cases, the API is not mixed with the paste, the tablet is printed then soaked in liquid suspension. However, using this method requires a lot of time to dry the tablet after printing and dry it again after soaking [51].

Printing temperature depends on the mixture, some mixtures can be even printed at room temperature. This method is efficient when the API or excipients are heat sensitive and FDM cannot be used. The main drawback is that it is time consuming. In some cases, the tablet should be dried for 24 hours after printing [62]. In addition, the risk of phase separation in the mixture should be taken into consideration for proper printing. If the mixture separates the dosage will not be consistent. Fan et al review the usage of direct ink writing in the biomedical field [78].

1.4.3 Using Selective Laser Sintering (SLS)

SLS can be used to make tablets. In this method, the API can be incorporated either prior printing or post printing. Moreover, solvents are not required when SLS is used, making the method time effective since there is no need to wait for drying. Additionally, the method utilizes powders so there is no need to form filaments.

If the drug is added before printing, a powder mixture of the API and excipient is prepared and added to the reservoir platform. Next the 3D model designed can be printed. However, when this method is selected, a specific excipient should be added to increase energy absorption and allow printability. Fina et Al (2017) added 3% gold sheen to the API and the polymer so the powder mixture can be sintered. The laser to sinter between layers is blue diode [42]. Salmoria et al (2012) researched the usage of

SLS using PCL with a hormone progesterone, to test different laser energy density and different particle size [79]. Since sintering polymers with API is challenging, most researches done on using SLS in the pharmaceutical industry, incorporate the drug in the tablet post-printing [80, 81].

1.4.4 Using Stereolithography Apparatus (SLA)

The usage of SLA for printing tablets is limited due to the lack of research on photopolymerized materials. In this method, the API and excipients (polymer and photoinitiator) are mixed to form a photoreactive solution that is then loaded to the printer and the models designed are printed. The advantage of using SLA to print tablets is that the printed model will have a high resolution. In addition, heat is not used in this method therefore more APIs can be incorporated in these printed tablets including heat sensitive drugs. However, the material is photopolymerized, further research is required to study the risks of photopolymerized objects. Mixing to get a photoreactive solution may take a long time. Wang et al (2016) mixed the solution for 8 hours to dissolve the photoiniator in the mixture). They evaluated the suitability of using SLA to print drug loaded tablets with modified release profile using polyethylene glycol diacrylate (PEGDA), diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide as a photo initiator, and 4-ASA and acetaminophen as the model drugs [82].

1.4.5 Using Binder Jetting

Binder jetting can also be used to print tablets, all powders are mixed, liquid binders are prepared and the tablet is printed. After printing, drying is required and it may take some time. Katstra et al (2000) printed complex devices testing different binder-powder combination [83]. The timing of the release is controlled by changing the quantity of the polymer. One advantage of binder jetting is the accuracy of deposition of binder leading to uniform content. Additionally, mechanical properties of a tablet printed by

binder jetting is similar to the one produced by the conventional method. Using this technology, it is possible to achieve immediate and controlled release. Rowe et al (2000) fabricated multi-mechanism oral dosage form using cellulose powder as the bulk for both sections, Eudragit E100 and ethanol for immediate release, Eudragit RLPO and acetone for extended release and encapsulating the model drug chlorpheniramine maleate and ethanol [84].

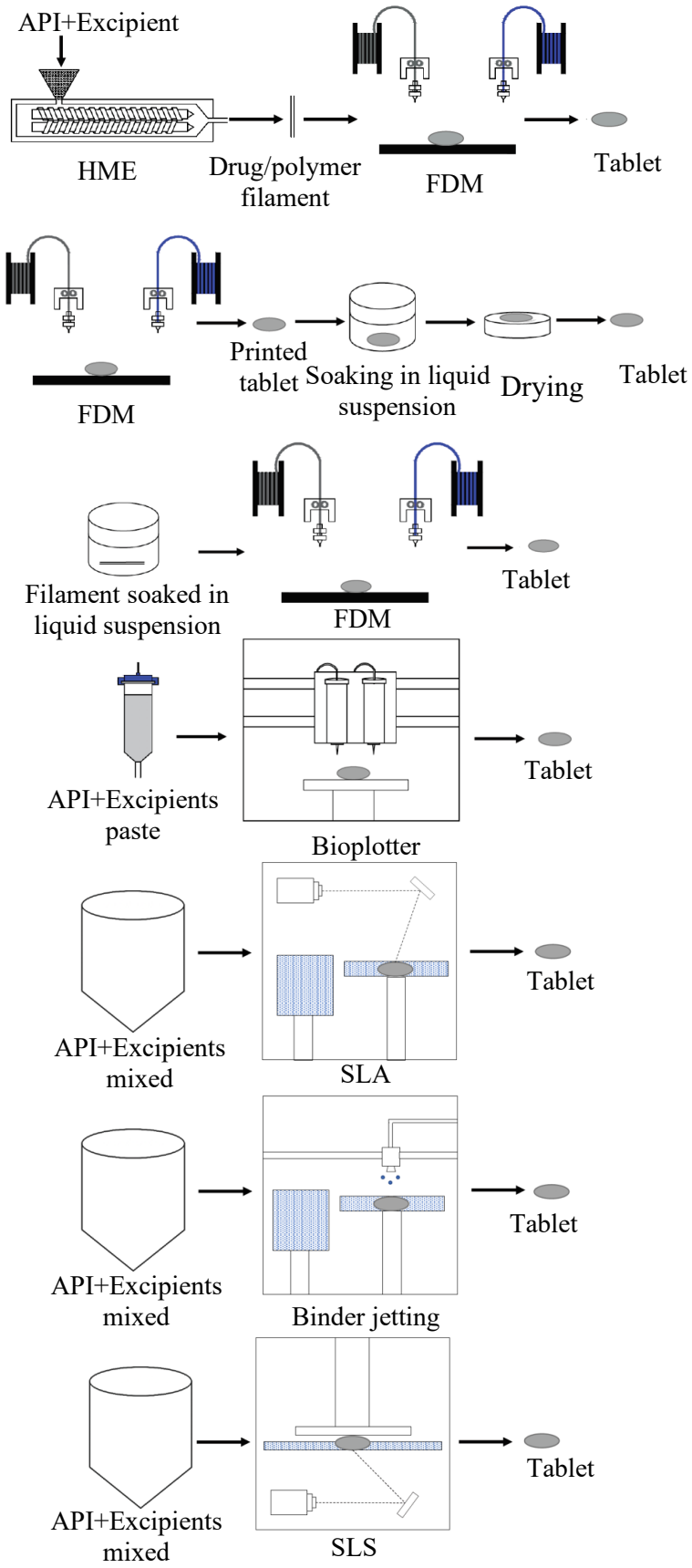


Figure 1.3 Processes using different 3D printing technologies to produce 3D printed tablets.

Table 1.3 Research Done on the Usage of 3D Printing Technologies to Form Tablets

Printing technology	Polymer	Model Drug	Reference
FDM of hot melt extruded loaded filament	PVA	Acetaminophen/Paracetamol	[64, 75, 76]
		Caffeine	[64, 76]
		Budesonide	[85]
		Aripiprazole	[61]
		Glipizide	[86]
		Hydrochlorothiazide	[87]
	Methacrylic polymer (Eudragit)	5-ASA	[88]
		Theophylline	[51, 89]
		Hydrochlorothiazide	[50]
		Captopril	[88]
		Prednisolone	[88]
		Paracetamol	[58]
	Cellulose based polymer (Hydroproxyl cellulose HPC)	Theophylline	[51]
		Acetaminophen	[90]
		Domperidone	[91]
	Cellulose based polymer (Hypromellose acetate succinate HPMCAS)	Paracetamol	[58]
	Polyvinylpyrrolidone (PVP)	Theophylline	[77]
		Dipyridamole	[77]
	Methacrylic polymer (Eudragit)	Deflazacort	[92]

FDM, API incorporated by soaking	Polycaprolactone (PCL)	Deflazacort	[92]
	Cellulose based polymer (cellulose acetate)	Atenolol	[62]
	Polyvinyl alcohol (PVA)	Prednisolone	[93]
		4-ASA	[59]
		5-ASA	[59]
		Curcumin	[94]
		Fluorescein	[95]
Bioplotter	Hydroxypropyl methylcellulose and Polyvinylpyrrolidone (PVP)	Ramipril	[62]
		Pravastatin	[62]
		Aspirin	[62]
		Hydrochlorothiazide	[62]
		Atenolol	[4]
	Hydroxypropyl methylcellulose and poly (acrylic acid) (PAA)	Guaifenesin	[96]
	Polyvinylpyrrolidone (PVP)	Paracetamol	[4]
Binder jetting	Colloidal silicon dioxide and polyvinylpyrrolidone (PVP)	Acetaminophen	[97]
	Methacrylic polymer (Eudragit)	Chlorpheniramine maleate	[84]
Selective laser sintering (SLS)	Polycaprolactone (PCL)	Progesterone	[79]
	Kollicoat IR (PVA and polyethylene glycol)	Paracetamol	[42]
SLA	PEGDA/PEG300	Paracetamol	[82]
		4-ASA	[82]

1.5 Challenges Facing 3D Printing

Despite being a very effective and promising method for the production of tablets, three-dimensional printing in the pharmaceutical industry faces a lot of challenges and it is still at the developing stage. Many problems should be overcome to move this technology from a theoretical method to an applicable method used in the industry. These obstacles can be related to the printer, to the ingredients in the formulation or to the regulations.

Many problems are associated with the printer used. Some technologies such as FDM and HME use heat to print and extrude. There are limited commercially available materials that can withstand high temperature. Materials are limited to non-heat sensitive APIs and excipients, and thermoplastic polymers which may not be pharmaceutically approved [98]. In addition, a filament is required when FDM is used. As discussed previously, the filament is either formed by soaking the filament in liquid suspension or by hot melt extrusion. When soaking is used there are two challenges, a limited amount of API can be incorporated, and the method required drying which is time consuming. Furthermore, one of the obstacles to overcome is print head clogging that may slow down the process. A very important factor in pharmaceutical production is to maintain reproducibility. When a semi solid, paste or binder is deposited, it is important to maintain a uniform flow. The print head either drops on demand or drops continuously [99]. When heat is used with FDM or HME, the polymer-drug combination is melted or partially melted and deposited on the platform. During a prolonged period of disuse, the polymer may dry inside the nozzle resulting in clogging. Studies about printability of materials to avoid clogging in required. When DIW is used, pastes are used, and it is more difficult to control the flow of semi solids through the nozzle resulting in unwanted drops. Finished 3D printed products may not be perfect

and may have rough surfaces. In some cases, postprocessing is needed such as drying, sintering or removal of support which may take some time. For binder jetting, migration of the binder in the powder or bleeding may occur. Excessive bleeding can result in a tablet with a rough surface. When DIW is used, post printing drying is sometimes required.

The most important question is: Are regulatory bodies able to handle this technology? There is a lack of regulations related to 3D printing for the production of oral solid dosages [1, 100, 101]. Although it can reshape the pharmaceutical industry, it needs more time and research to grow. Regulatory bodies like the FDA have instructions and supervision over for all methods, processes, equipment and ingredients used. 3D printers are advanced equipment and they require a lot of research to be used in application. All printers should be kept in a sterile environment, it should be guaranteed that all the parts are sterile including the nozzle, gear and platform. To achieve products with high performance and reproducibility, much more research should be done to understand and optimize printing parameters such as infill density, extrusion speed, temperature, pressure, layer height and sintering speed [9]. Processing of the drug is different than the conventional compression method, further understanding is necessary for the API including its solubility, stability, crystal morphology and thermal stability [99]. Additionally, more research should be done to study the interaction of the API with the polymers.

There are other challenges that are not related to the process. 3D printing can lead to personalized, made on demand drug products that are printed by healthcare providers based on the patients' needs [102]. It is also a challenge to train all providers to be able to use the printers. Pharmacies and hospitals should have the right environment for tablet production to avoid any contamination. In addition, all filaments

and mixtures should be commercially available in different dosages. This create a challenge to pharmaceutical companies to switch from mass production of oral solid dosages to the production of mixtures and filaments for individualized production. Moreover, all CAD designs should be modeled with determined release profiles.

CHAPTER 2

MATERIALS AND METHODS

2.1 Materials

Polyvinyl alcohol (PVA) filament (Ultimaker) with a diameter of 2.85 mm was used in this study. Provider recommended printing temperature for this PVA is in the range of 210-225 °C. Both APIs, acetaminophen (molecular weight equal to 151.16 g/mol) and caffeine (molecular weight equal to 194.19 g/mol), are purchased from Sigma-Aldrich. The chemical structure of the PVA, acetaminophen and caffeine are given in Figure 2.1.

PVA powder with average molecular weight 85,000-124,000 and 146,000-186,000 were also purchased from Sigma-Aldrich for further testing.

For the gear modification, SYLGARD™ 184 Silicone Elastomer Kit (elastomer and curing agent, Dow Corning Co.) was used.

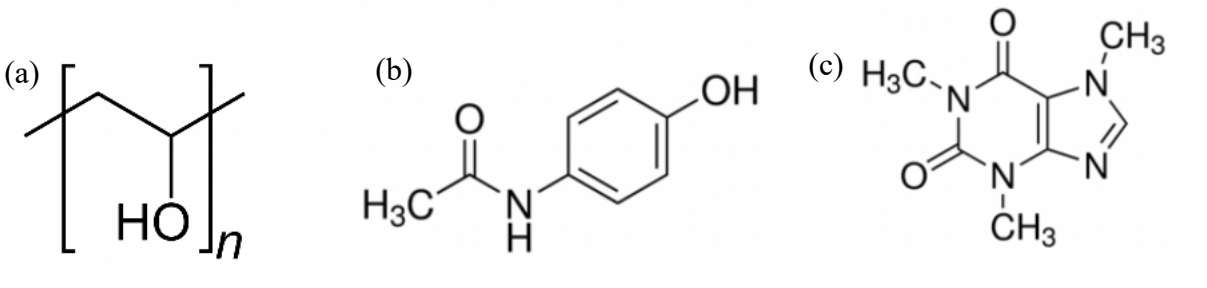


Figure 2.1 Chemical structures of (a) PVA, (b) acetaminophen, and (c) caffeine.

2.2 Methods

2.2.1 Hot Melt Extrusion

PVA filaments were cut using a filament cutter, and grinded using a coffee grinder. Next, the grinded PVA was sieved using an 800 µm sieve. The API was added to the powder and the mixture was hand mixed. The theoretical content of the API was adjusted to be 10 wt%. The mixture was gradually fed to the hot melt extruder. All temperatures used in the process are summarized in Figure 2.2. The rotation speed was fixed at 150 rpm.

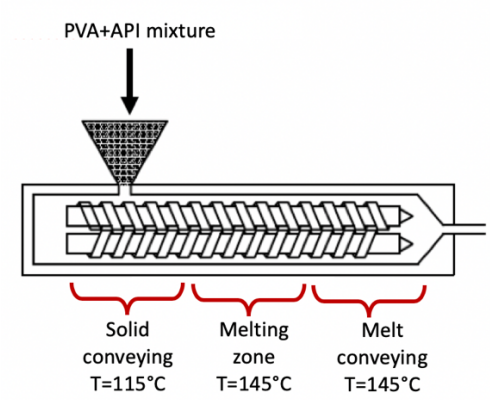


Figure 2.2 Figure representing the set temperature values used in the twin-screw hot melt extrusion of PVA-based filaments.

2.2.2 Printing Tablets

3D models were first designed using Fusion360 (Autodesk, USA) and saved as an stl file. The model was then sliced using the printer software. The filaments prepared were loaded in the printer, then the models were printed at a temperature of 180°C, a layer height of 0.15 mm, a speed of 5 mm/s and an infill of 100%. No support, raft or wall were used during printing. The printer used was a Flashforge FDM Creator Pro dual extruder 3D printer (Flashforge, USA) equipped with a 0.4 mm nozzle.

2.2.3 Thermal Analysis

Since the filaments and mixture underwent processes under high temperature, thermal analysis was done to investigate their behavior with increasing temperature. Samples

tested were commercially available PVA, powder PVA, caffeine, acetaminophen, extruded filaments, and the filaments after printing.

Thermogravimetric analysis (TGA) was done using TGA 8000 from Perkin Elmer. Samples were heated in aluminum pans from 30°C to 300°C, at a rate of 10°C/min under nitrogen gas. The approximate weight added was in the range of 10-18 mg. In addition, differential scanning calorimetry was performed using DSC 4000 from Perkin Elmer. The heating rate was 10°C/min. Samples (6-8 mg) were added to aluminum pans with lids. Heat-cool-heat scan is done by heating to 250°C, cooling to 30°C, then heating again to 250°C.

2.2.4 Printing Optimization and Quality Checking

Printing parameters such as the printing speed, extrusion ratio, printing with wall, and path width were varied to determine the optimum printing conditions that minimizes porosity. These tests were done using the standard control tablet design.

2.2.5 Characterization of Tablet Morphology

The physical dimensions, such as the diameter and the thickness, of the tablets were measured using a digital caliper. All tablets printed were also weighed to analyze the variation between prints.

Pictures of the tablets were taken using a Nikon COOLPIX B500 digital camera. Optical microscopy images were taken using the x20 magnification to look at the spacing between the printed struts.

2.2.6 Determination of Drug Loading

Samples were taken after the full dissolution of all models in water at 37°C. Samples are analyzed using the plate reader at a wavelength of 275 nm. The measured drug loading was then compared with the theoretical drug loading of 10% of the total PVA+Acetaminophen weight.

2.2.7 Micro CT Scanning

An X-ray micro computed tomography scanner skyscan 1275 (Bruker, USA) was used to visualize the printed tablets. The inner structure, porosity and density were inspected to make sure that the print was successful. NRecon and CTvox softwares are used after scanning to construct and form the 3D model.

2.2.8 X-Ray Powder Diffraction (XRPD)

X-ray diffractometer EMPYREAN (PANanalytical, Netherland) was used to determine the physical form of the drugs in the polymeric mixture. Samples tested were caffeine, acetaminophen, printed PVA+caffeine and printed PVA+acetaminophen. Films that were 23 mm in diameter and 1 mm in width were printed using the extruded filaments to fabricate the printed samples. Scanning is done from 2theta of 5 to 60° and a step of 0.013° using a Cu X-ray source.

2.2.9 Rheology

Disks (25 mm in diameter and 1 mm in width) were printed using the FDM printer. Rheological properties of the samples were tested by doing a temperature sweep from 80 to 200 °C at a rate of 5°C/min. The loading force is maintained at 1N and the stress at 100 Pa.

2.2.10 Dissolution Test

Drug release test was carried out using a Distek dissolution premier 6100 (Distek, USA). Printed tablets were randomly selected and placed into sinkers. The paddles had a fixed speed of 100 rpm and were immerged in vessels containing 900mL of water. Tests were conducted in triplicates. During dissolution tests, 2 mL of samples were collected every 1 minute for the first 10 minutes, then every 3 minutes for the following 10 minutes, then every 5 minutes for the following 40 minutes, then every 10 minutes for the next 40 mins, and finally every 30 minutes until the tablet was fully dissolved.

All samples were then pipetted into a 96 well FALCON plate and the plate reader was used to detect the absorbance at 275 nm at room temperature.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Forming Drug Loaded Filaments

PVA powders with two different molecular weights were tested to directly print PVA using extrusion-based direct ink writing (DIW) printer. Direct melt printing attempts were not successful due to extensive degradation of the PVA. The same problem as also encountered when PVA was directly extruded using HME. Our initial results showed that it was not possible to use these powders alone and other excipients were needed. Thus, to move the project faster, we decided to use the commercially available PVA filaments in this study. As shown in Figure 3.1, PVA filaments were cut, sieved and used in powder form for HME.

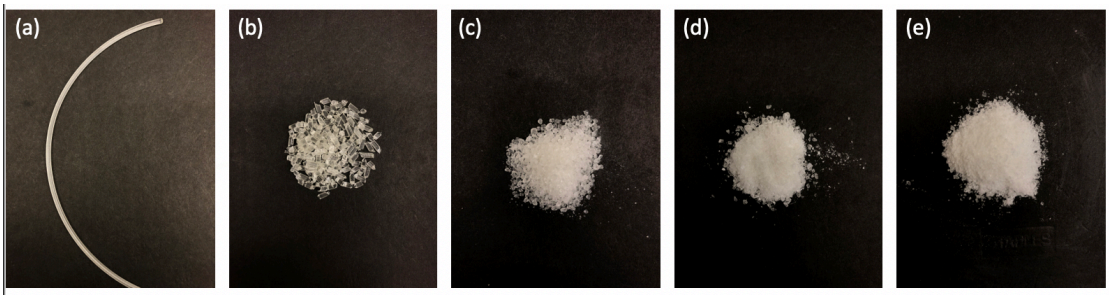
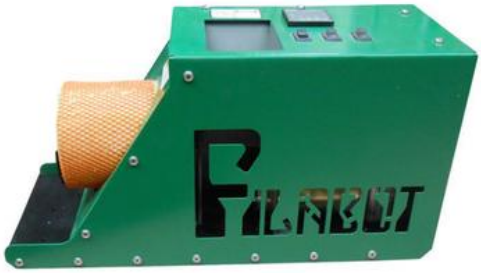


Figure 3.1 Steps to prepare the powder mixture (a) commercially available PVA filament, (b) cut PVA filaments, (c) ground PVA, (d) sieved PVA powder, and (e) PVA mixed with acetaminophen.

Using fused deposition modeling requires polymers in the form of filaments with correct filament diameter determined by the print head size. To form filaments, we first used a tabletop hot melt extruder with a single screw. Due to the hygroscopic property and moisture sensitivity of PVA, and the lack of compressibility using single screw extruder, it was not possible to get filaments using this apparatus. For that reason, hot melt extrusion with twin screw was tested and was shown successful to extrude the PVA filaments with API. Figure 3.2 represents both of the equipment tested. First

extrusion was tested at 160°C, however extrusion was too fast, and the filaments were too small. After trying a wide range of temperatures, we finally decided to use 145°C with a rotational speed of 150 rpm. The extrusion was smooth, and the speed resulted in an acceptable filament size, and the materials did not degrade during this process.

(a)



(b)

Figure 2.2 Hot melt extruders (a) Single screw extruder from Filabot, (b) Twin screw extruder from Leistritz

3.2 Characterization of Filaments and Powders

Filaments were extruded as mentioned above and a caliper is used to measure its diameter. Filament diameter was found to be in the range of 1.35 to 1.45 mm. MicroCT images shown in Figure 3.3 proved that the surface of the filaments was uniform and there were no pores in the filament.

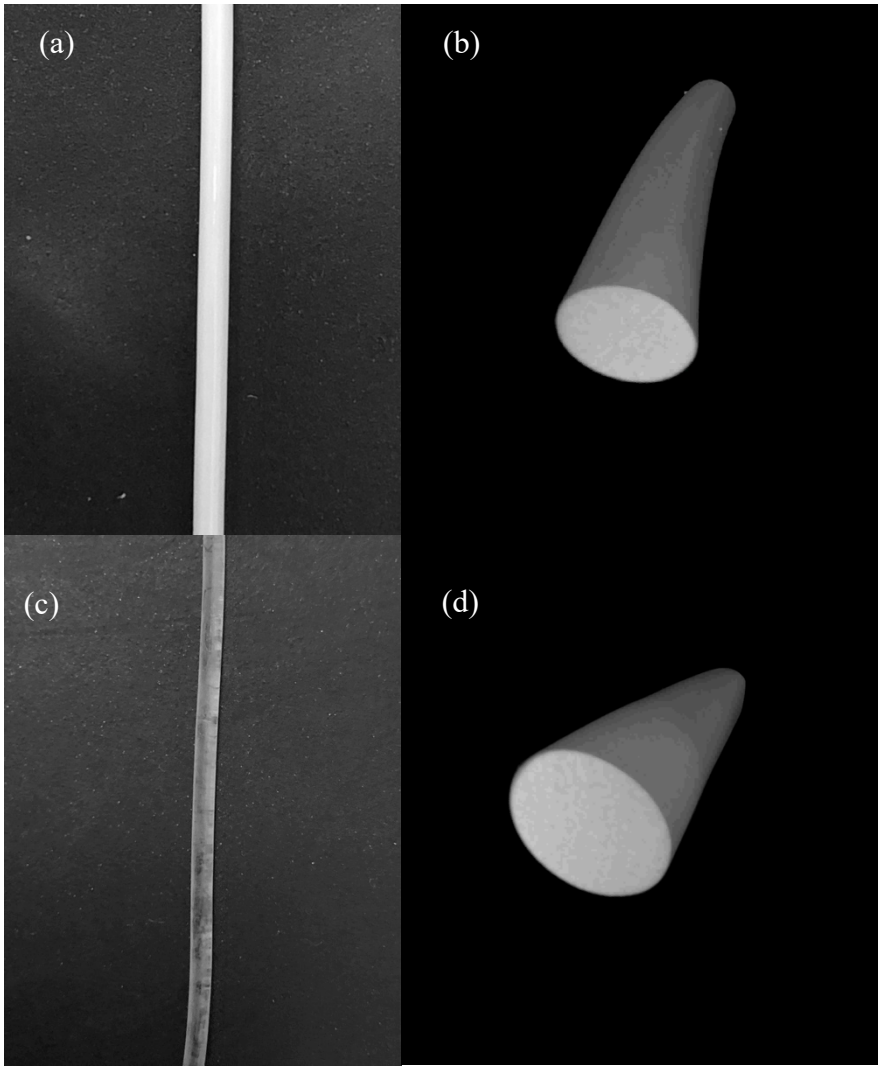


Figure 3.3 Images of extruded filaments: (a) picture of PVA+Caffeine filament, (b) micro CT image of PVA+Caffeine filament, (c) picture of PVA+Acetaminophen filament, and (d) micro CT image of PVA+Acetaminophen filament

DSC was done to explore the thermal behavior of the materials to define the extrusion and the printing temperatures. Heat/cool/heat is done to erase previous thermal history. First heating provides information about the materials as it is. Cooling gives information about crystallization where the chains have enough energy to form ordered arrangement and crystallize. The second heating shows the real thermal properties of the material disregarding thermal history. However, according to Figure 3.4a, for the acetaminophen sample, crystallization happened at the second heating curve. This process is called cold crystallization where a sample that has previously been cooled very quickly and has had no time to crystallize. Furthermore, caffeine underwent sublimation on the first heating where the substance went directly from solid to gas without passing through the liquid phase. This process is based on the material phase diagram. Sublimation will not affect extrusion or printing of the tablet because at atmospheric pressure, air molecules push the evaporating molecules to the condensed phase. Condensation only appeared in the DSC data where the experiment was done under nitrogen gas.

The importance to do the heat/cool/heat in this case is to analyze the thermal history of all the materials to understand the effect of heat on the samples and to identify the melting point or range to be able to know the extrusion and printing temperature. Both should be done around the melting temperature of the powders. According to Figure 3.4, acetaminophen melts at 160°C, caffeine melts at 230°C and, PVA melts at 160-190°C. Therefore, as explained previously, extrusion was done by heating at 160°C. From the DSC data, it is shown that PVA powder, PVA extruded and PVA mixed with the APIs had a broad melting range, and the APIs alone had a melting point. This was also confirmed by the XRD data shown in Figure 3.5. API did not appear in

the diffractograms of the formulations. Although APIs are crystalline, they became amorphous in the matrix with PVA.

TGA data shown in Figure 3.6 predicted that no degradation will occur for the API, the polymer and the extruded filaments at the temperatures used in all the experiments. All these materials underwent high temperature processes, such that the PVA and the API were extruded at 145°C, and the filament was printed at 180°C. Thus, we confirmed that all of the materials used were stable when the temperature was lower than 200°C. The weight loss was lower than 10% for the PVA before and after extrusion, and for the filament (PVA with drug) and the printed form. Some of the data showed a small decrease of the weight at around 100°C due to the moisture content. PVA is hydroscopic and absorbs water, thus at 100°C the water evaporates which leads to this decrease. For both APIs, the weight loss was 80% after heating to 300°C, however all of the proposed experiments were done at a temperature lower than 300°C.

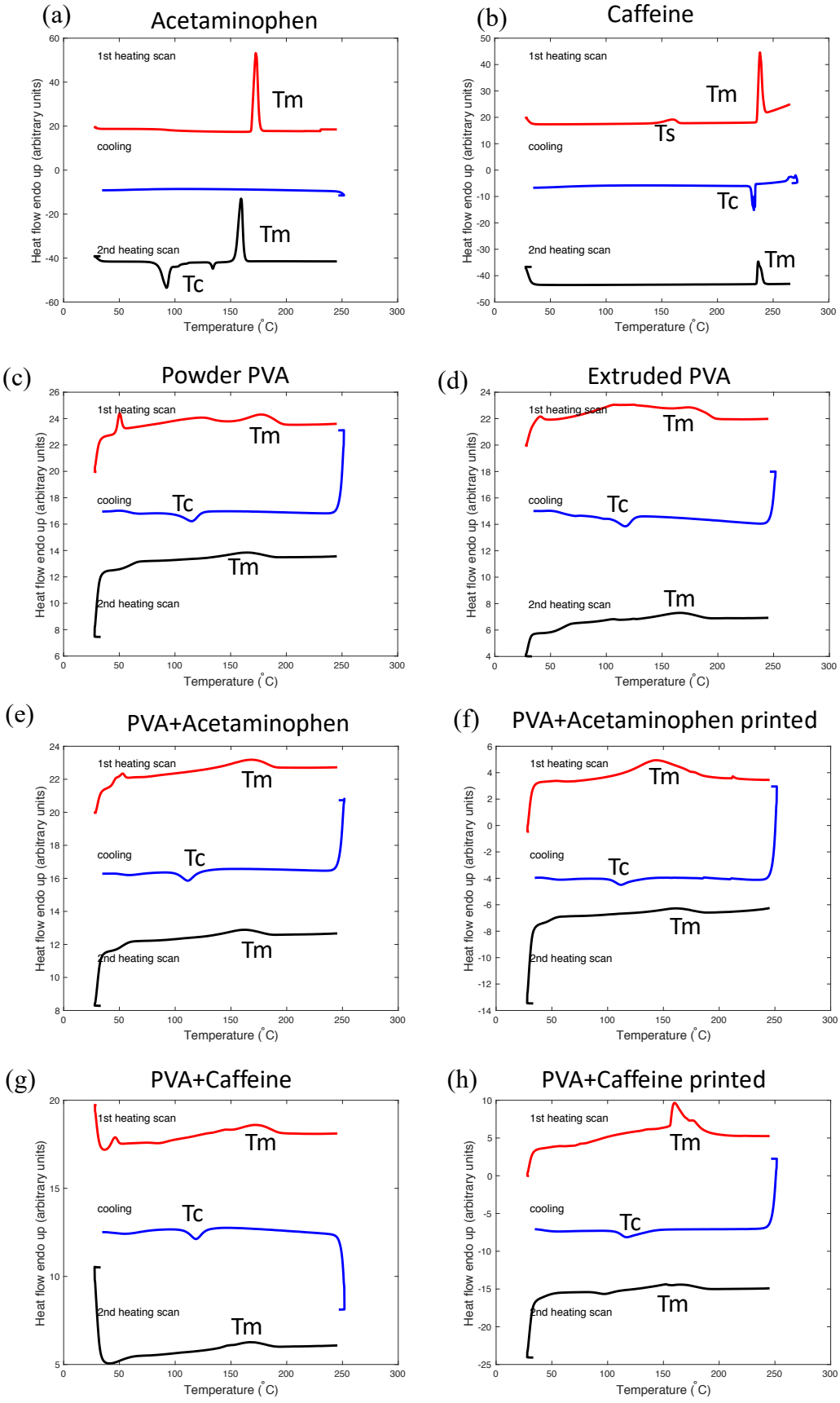


Figure 3.4 DSC thermal data for (a) acetaminophen, (b) caffeine, (c) powder PVA, (d) extruded PVA, (e) PVA+acetaminophen filament, (f) PVA+acetaminophen

printed, (g) PVA+caffeine filament, and (h) PVA+caffeine printed. Tm: melting temperature, Tc: crystallization temperature, Ts: Sublimation temperature.

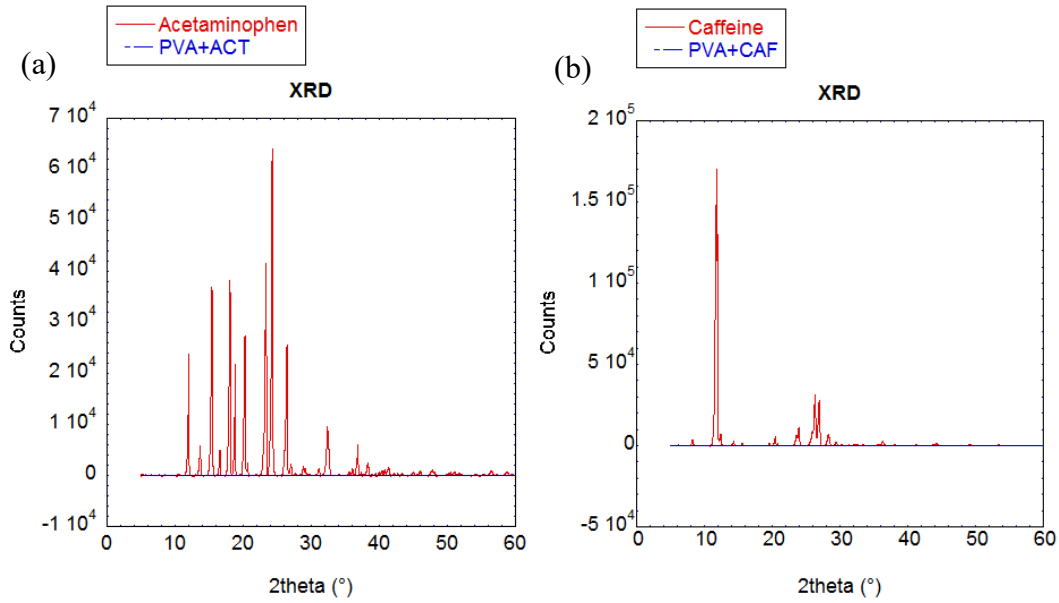


Figure 3.5 XRD data for (a) acetaminophen powder and PVA+acetaminophen printed film, (b) caffeine powder and PVA+caffeine printed film.

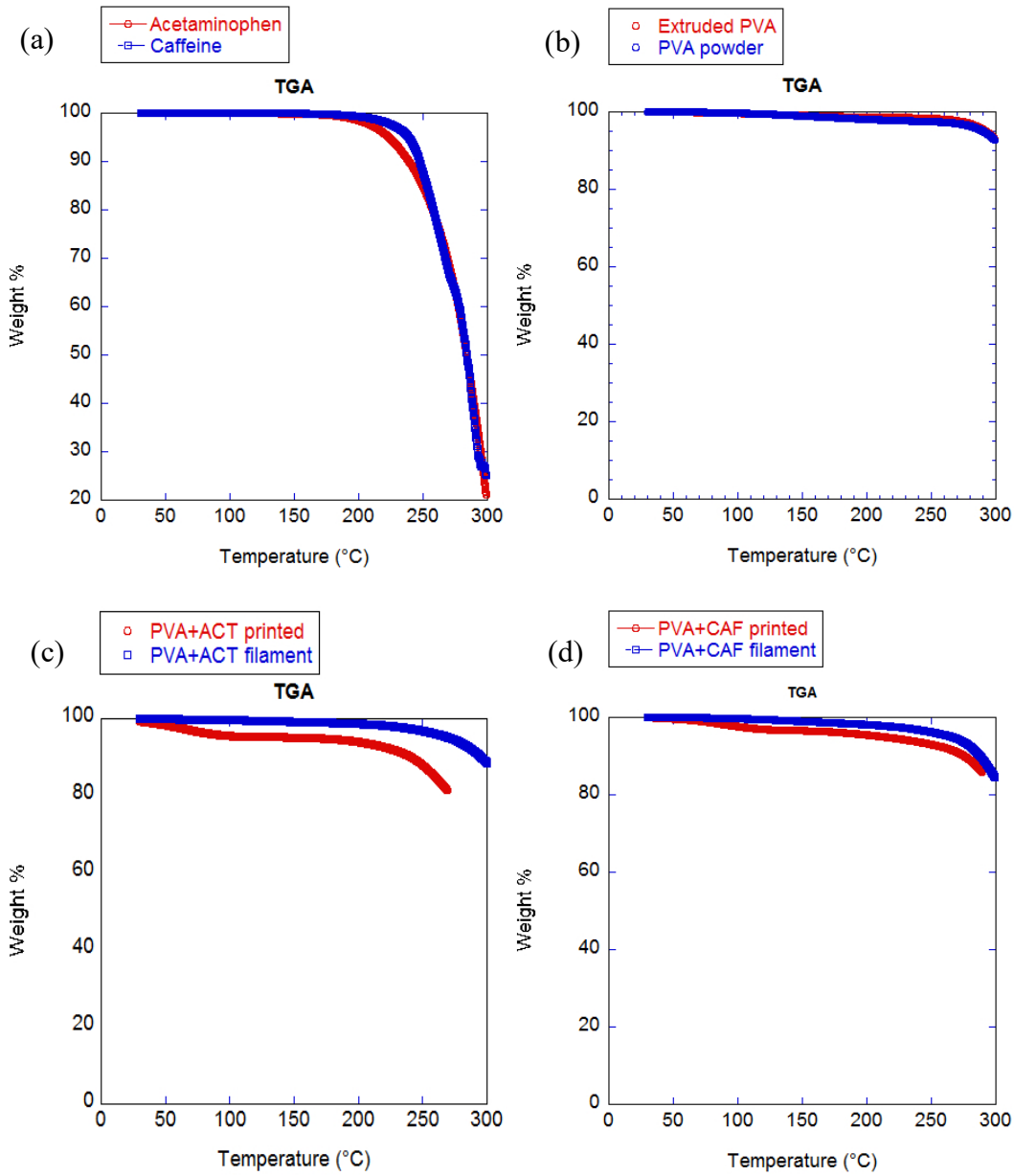


Figure 3.6 TGA data for (a) the APIs: Acetaminophen and caffeine, (b) the polymer powder and extruded, (c) PVA and acetaminophen filament and printed form, (d) PVA and caffeine filament and printed form.

3.3 3D Printing of Drug Loaded Tablets

3.3.1 Design of Tablets

3D models were designed using Fusion360 software. First, tablets with holes were designed. All of them had the same volume and theoretically should have the same amount of drug. Figure 3.7 represents the models designed. The tablets are circular with a diameter of 12 mm and a thickness of 2 mm. The higher the surface area in contact with the water, the higher the dissolution rate of the tablet. The goal behind printing these tablets was to achieve an immediate release of the drug. Immediate release drugs are used to give on fast onset of drug action. It allows the drug to dissolve in the gastrointestinal contents without the intention of delaying or releasing. These tablets are usually used for immediate effect such as painkilling.

The second model set designed were the tablets with outer layer of PVA to delay the release as shown in Figure 3.8. The goal is to delay the release of the tablets. The outer PVA acts as a coat that will dissolve first delaying the dissolution of the drug. The higher the coating thickness the higher the lag time for the API. Delaying the release is done to control when and where the drug is released. Furthermore, it also protects the stomach from irritation by the drug.

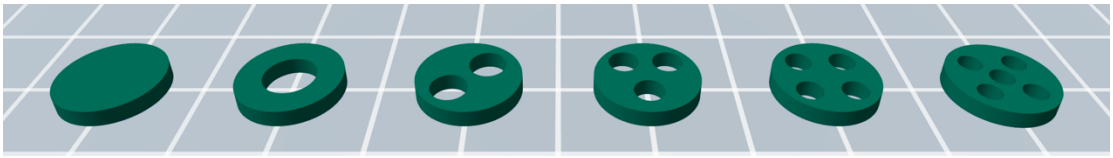


Figure 3.7 Designs of circular tablets with holes

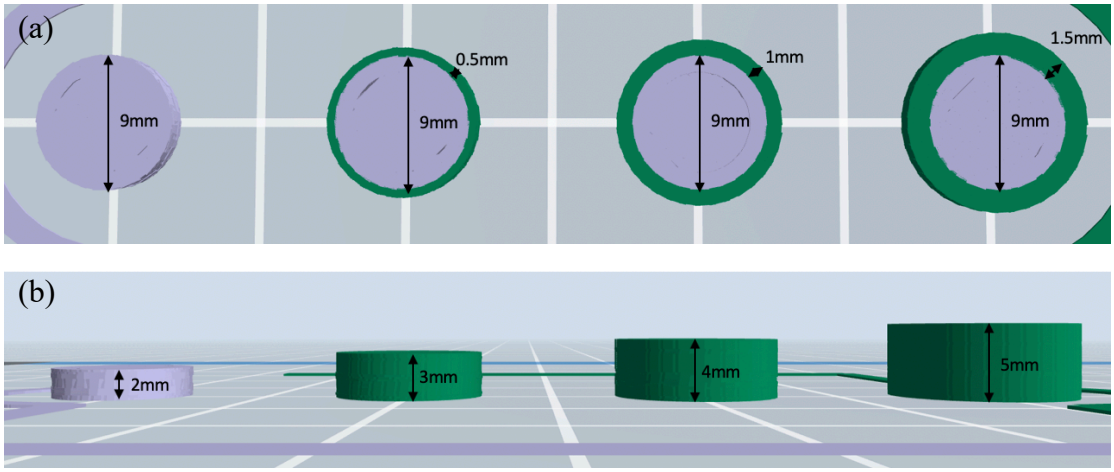


Figure 3.8 Designs of delay released tablets (a) cross section, (b) side view. The green represents the PVA and the grey represents the PVA+API

3.3.2 3D Printing and Optimization

The Flashforge FDM printer used in this study is compatible with filaments of 1.75 mm, therefore, the printer had to be modified to be able to grab and print smaller filaments we fabricated. A mixture of 1:1 PDMS and curing agent was prepared, and the gears were coated with a thin layer then was put in the oven at 70°C overnight. Although this method was effective to create a softer coating and allowed printing of the smaller filaments we found that the PDMS coating wore out easily and the gear had to be recoated after every other print. A second method was tested by putting a small rubber band around the gear. This method worked much better as the rubber bands did not wear out and were not affected by high temperature. Figure 3.9 shows the gear before and after modification. The diameter of the gear was 9.7 to 10.2 mm, decreasing the gap to grab the filament from 1.15 to 0.9 mm.

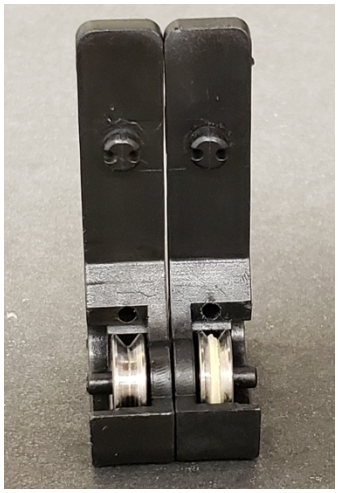


Figure 3.9 Left to right; unmodified and modified gear

Since the filaments were smaller than usual, optimization was required to minimize the distance between printed struts. All the printing tests were done using the PVA+acetaminophen control tablet. First, the extrusion ratio or the percentage of material extruded was increased to 125%. When the ratio was higher, we observed less pores because more material was deposited. Next, the path width was modified as shown in Figure 3.10. It is proved that the lower the path width the better the printing. For the surface view, both path width tested had similar spacing. When looking at the shells, the model with a path width of 0.35 mm had less spacing. To improve the quality even more, different printing speeds were tested. The lower the speed, the smaller the distance between the struts. However, the print would take longer time and the filament would stay longer in the gear/heating region and might become soft. Printing speed of 1 mm/s and 3 mm/s were also tested but printing was not successful, the filaments become soft and the gears cannot grab them. It is shown in Figure 3.11 that when the speed is 5 mm/s, the struts were connected to each other and the print take 5-20 minutes depending on the model. Our results showed that the printing speed has a great effect on the print quality.

As illustrated in the micro CT images in Figure 3.12, the optimization had a major effect on the quality of the print and the infill. However, there were some spacing between the inner structure and the outer shells. To try to minimize it, two different numbers of shells were tested to check if we could improve the printing more for the outer part. Nonetheless, it was shown that for 10 shells, the shells look good, but the inner part had a lot of pores, as can be seen from Figure 3.13. Therefore, 3 shells were still better than a higher number of shells. The optimum printing parameters were summarized in Table 3.1.

For the second model set, where PVA+acetaminophen is coated with a layer of PVA only, all the printing properties were kept the same. However, as shown in Figure 3.14 that a wall was required to get a successful print. When multiple printing heads were used, the nozzle was kept at the temperature set. While one nozzle was printing the other was standing by. However, the one standing maintained a high temperature so the material may continue to melt down resulting in oozing. The wall was meant to minimize oozing by scraping off excess material and cleaning the nozzle tip.

All tablets were printed with the optimum parameters mentioned above (Table 3.1), Figure 3.15 shows the tablets with different numbers of holes while maintaining the same volume, and Figure 3.16 shows the tablets printed with different thicknesses of outer PVA coating. Printing was a smooth and successful process. A double-sided tape was used to improve the adhesiveness of the tablet on the printing platform.

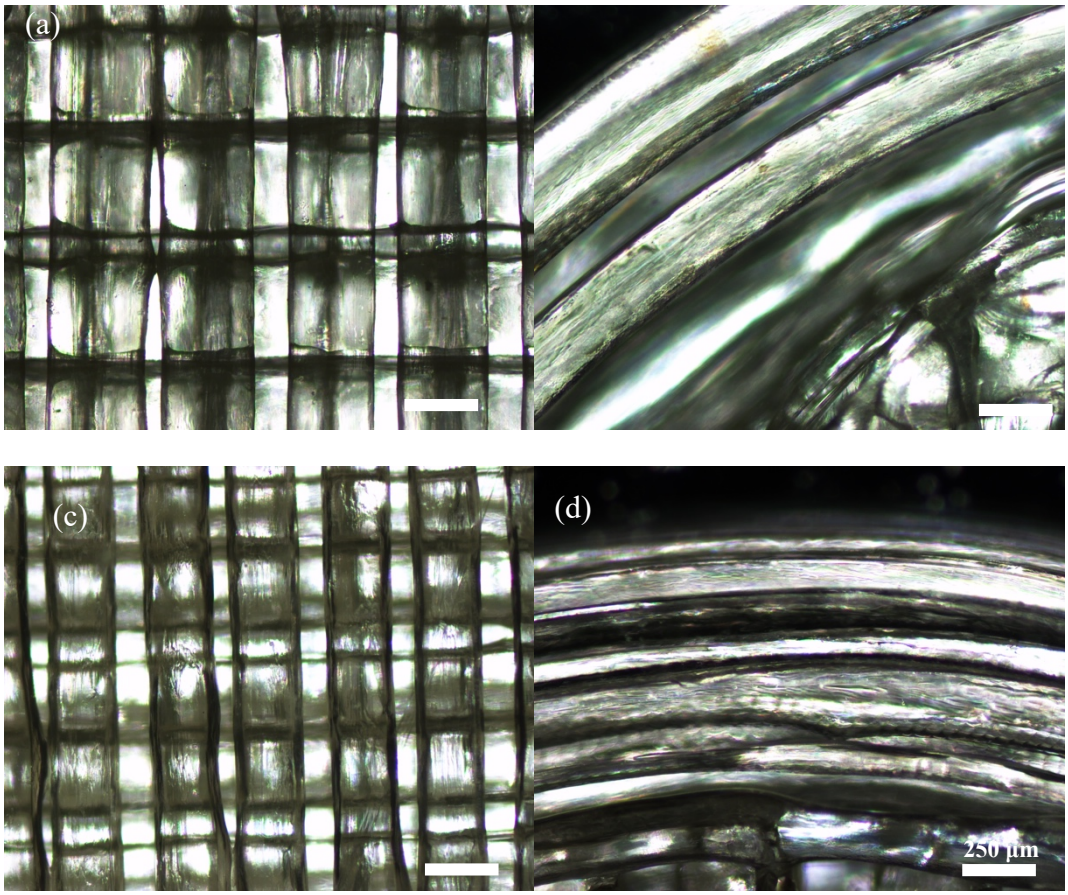


Figure 3.10 Optical microscope images of the printed tablets at a speed of 20 mm/s, and an extrusion ratio of 125%. (a) Surface image with a path width of 0.45 mm, (b) shell image with a path width of 0.45 mm, (c) surface image with a path width of 0.35 mm, and (d) shell image with a path width of 0.45 mm. All scale bars are 250 µm.

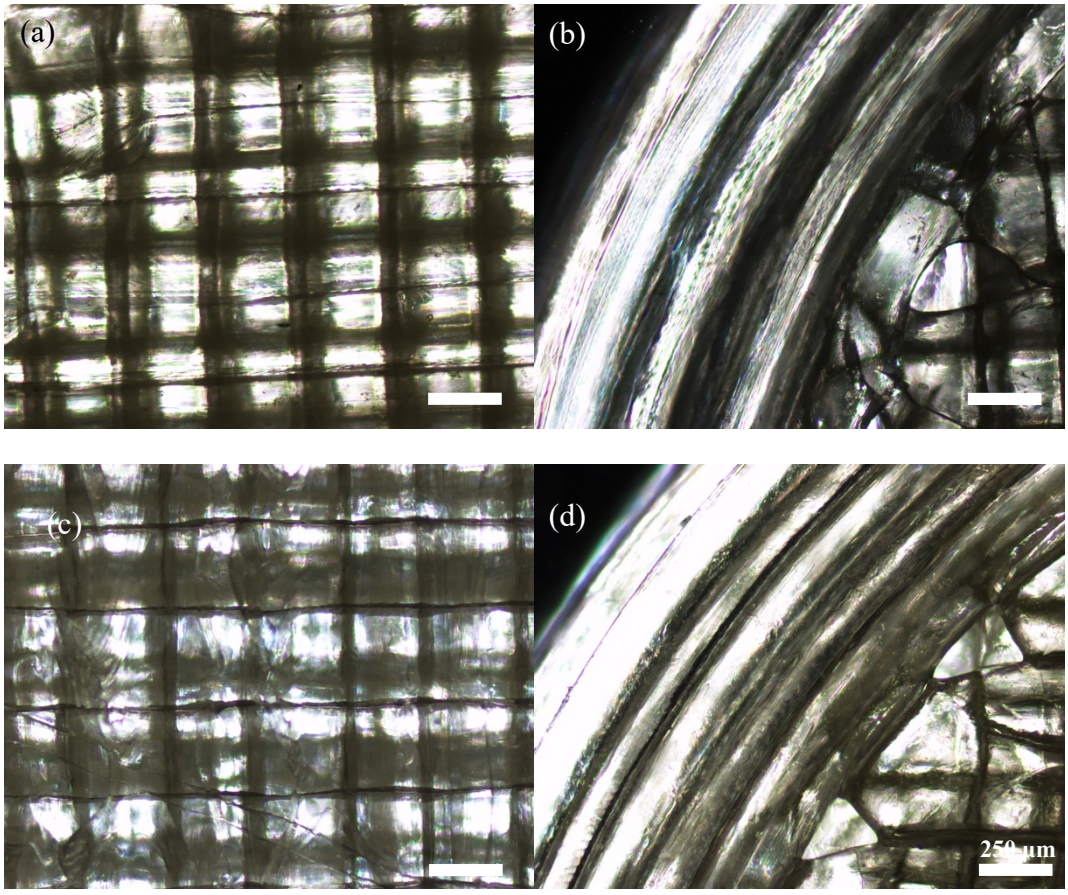


Figure 3.11 Optical microscope images of the printed tablets with a path width of 0.35 mm and an extrusion ratio of 125%. (a) Surface image with printing speed of 10 mm/s, (b) shell image with a printing speed of 10 mm/s, (c) surface image with a printing speed of 5 mm/s, and (d) shell image with printing speed of 5 mm/s. All scale bars are 250 µm.

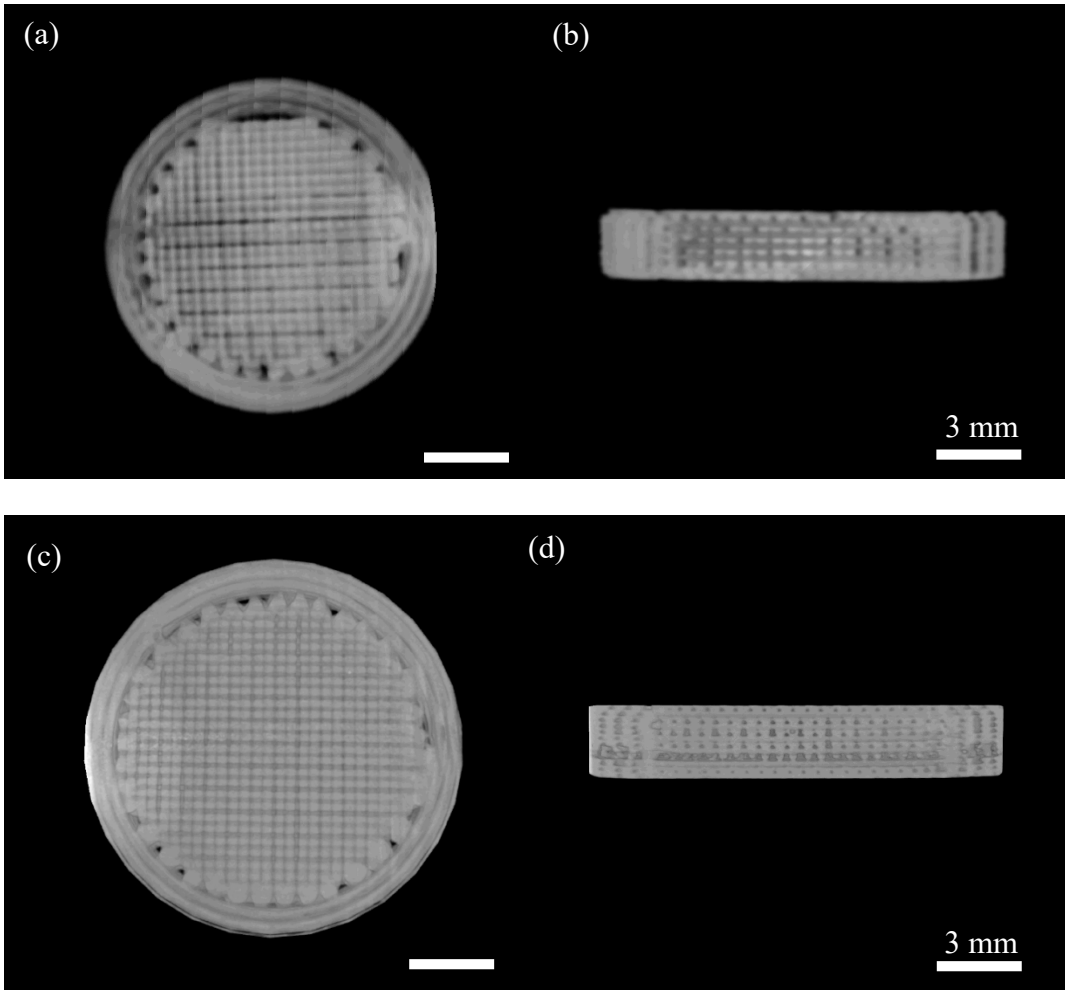


Figure 3.12 Micro CT images of PVA+Acetaminophen tablets: (a) surface before optimization, (b) Cross section before optimization, (c) surface after optimization, (d) cross section after optimization. All scale bars are 3 mm.

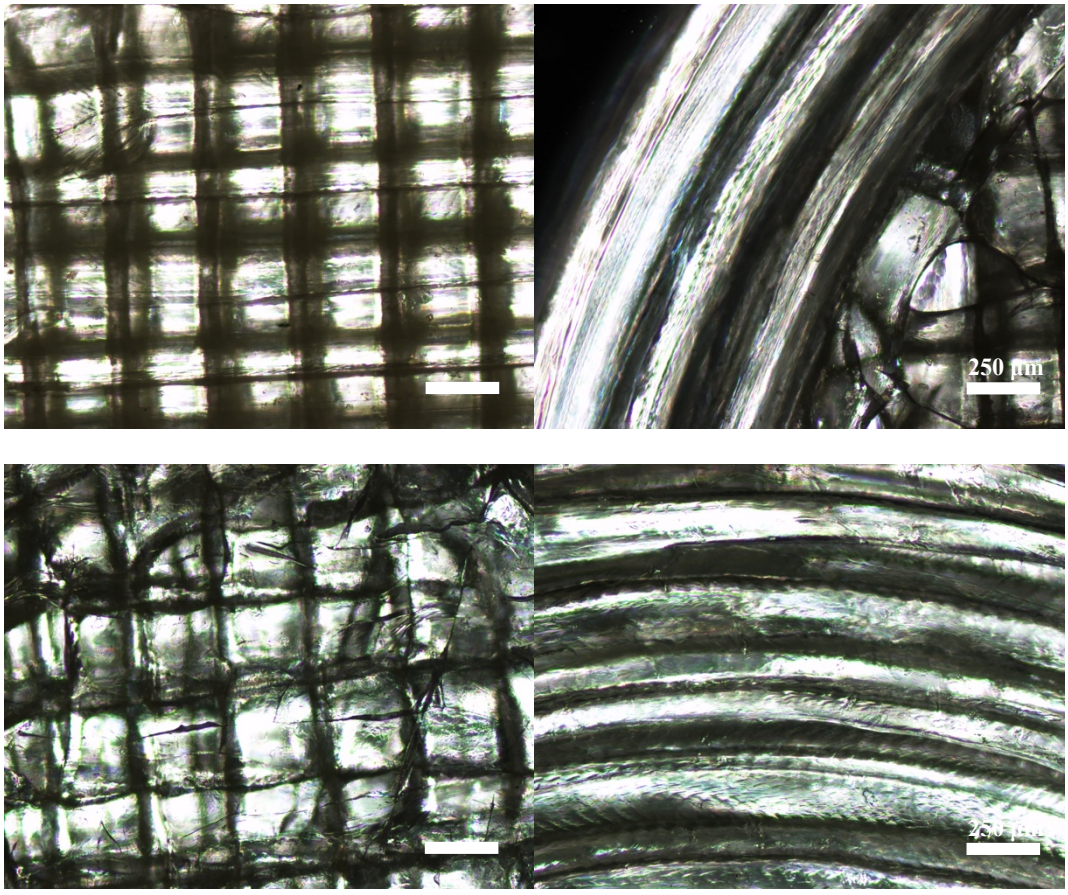


Figure 3.13 Optical microscope images of the printed tablets with a path width of 0.35 mm, an extrusion ratio of 125%, and a printing speed of 5 mm/s. (a) surface image with 3 outer shells, (b) image of a tablet with 3 outer shells, (c) surface image with 10 outer shells, and (d) image of a tablet with 10 outer shells. All scale bars are 250 µm.

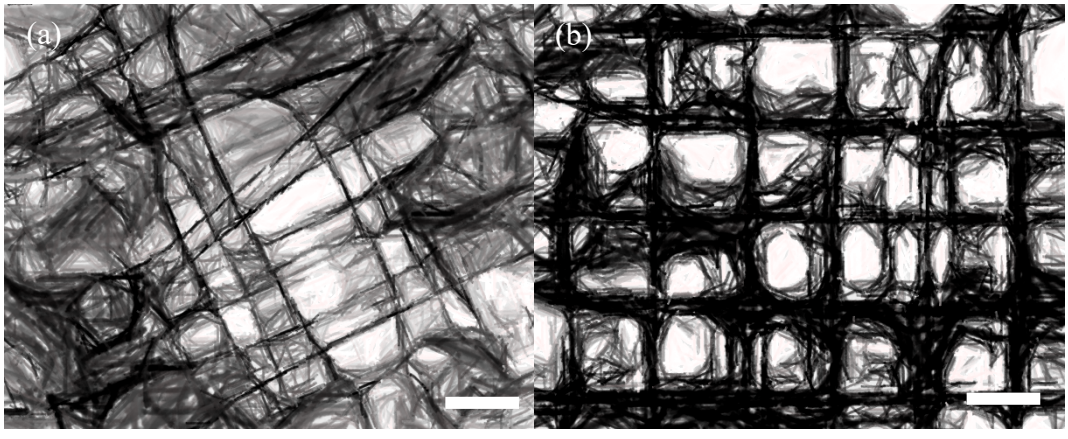


Figure 3.14 Optical images of the tablets printed with two materials, PVA and PVA+Acetaminophen, (a) printing without a wall, (b) printing with a wall. All scale bars are 250 µm.

Table 3.1 All Optimum Printing Parameters to Minimize Pores in the 3D Printed Tablet.

Temperature	Layer height	Printing speed	Number of shells	Infill density	Path width	Extrusion ratio
180°C	0.15 mm	5 mm/s	3	100%	0.35 mm	125%

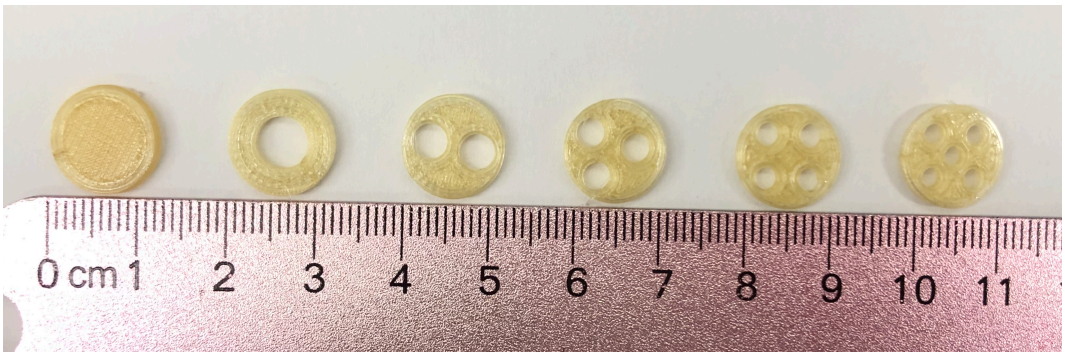


Figure 3.15: Pictures of the 3D printed tablets with different number of holes. Hole volume was kept the same.

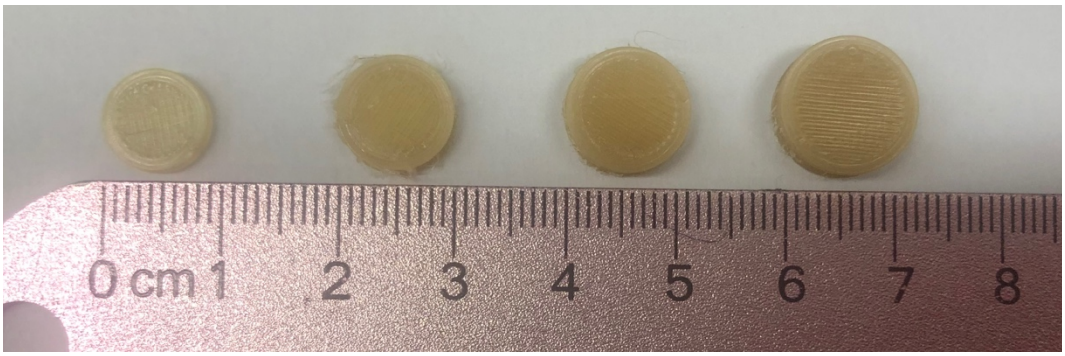


Figure 3.16. Pictures of the 3D printed tablets with outer PVA coating. From left to right: no coating, coated with 0.5 mm PVA, coated with 1 mm PVA, and coated with 1.5 mm PVA.

3.3.3 Flow Properties

As mentioned above, the filaments made have a broad melting point. Rheology is done to see at which temperature the viscous modulus become higher than the elastic modulus. Note that the solid to melt transition begins when elastic modulus intersects

with the viscous modulus. PVA becomes melt and behaves like a viscous liquid when viscous modulus is greater than the elastic modulus. For PVA, the switch happened at 180°C based on Figure 3.17, and PVA was usually printed at 200°C. This switch happened at 165°C for PVA+acetaminophen. After this temperature the mixtures had better flowability and printability. Thus, 180°C was a good printing temperature.

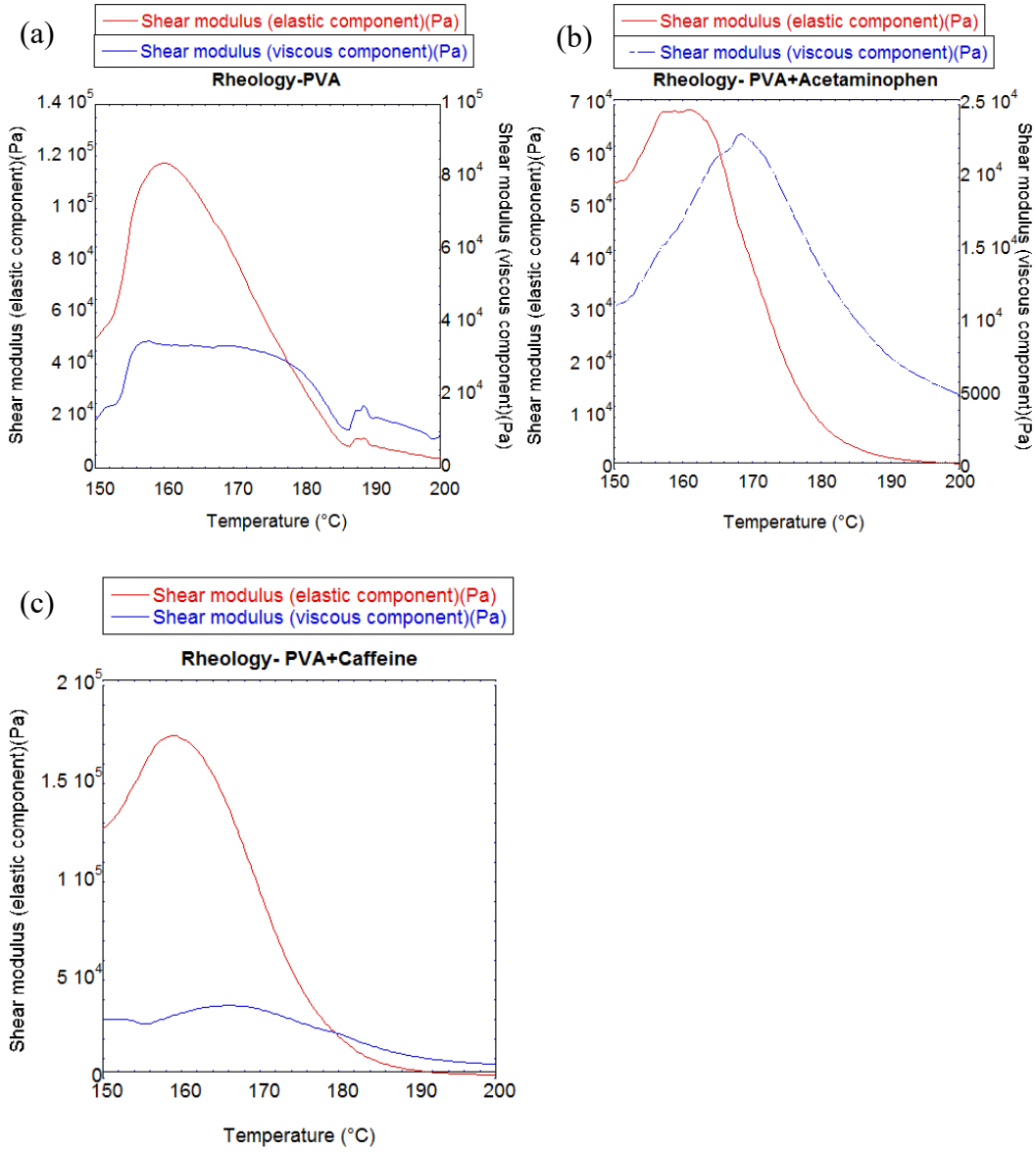


Figure 3.17 Rheology data for (a) PVA, (b) PVA+Acetaminophen and (c) PVA+Caffeine

3.4 Characterization of Printed Tablets

All tablets printed were weighed to make sure they had the same weight. Table 3.2 shows the weights, height and diameter of the printed tablets. In addition, it also shows the final drug percentage of the tablets that was tested to check if it matched the theoretical value (10%). It is shown that the tablets have minor differences regarding the shape, the weight and the drug content.

Analysis of the drug content for the tablets demonstrated that HME and FDM can lead to a variation in the amount of API found. The average drug loading was found to be 10±3%. This could be further improved by mixing the powders better prior the formation of filaments.

Table 3.2 Weight, Thickness, Diameter, and Percentage of Acetaminophen of all the Models Printed for 3 Randomly Selected Samples for Each

	Weight (g)	Thickness (mm)	Diameter (mm)	% Acetaminophen
Standard	0.15±0.004	2.05±0.005	11.7±0.02	7.273
1 hole	0.194±0.002	1.8±0.003	11.56±0.01	7.029
2 holes	0.132±0.001	1.9±0.01	11.58±0.01	8.264
3 holes	0.187±0.01	-	11.54±0.03	10.209
uncoated tablet	0.141±0.003	1.84±0.02	8.87±0.03	7.737
tablet coated with 0.5 mm	0.254±0.002	2.9±0.01	9.89±0.02	9.671
tablet coated with 1 mm	0.416±0.003	4.46±0.02	10.79±0.02	11.605
tablet coated with 1.5 mm	0.662±0.005	5.48±0.02	11.88±0.02	9.671

3.5 Dissolution Test

The dissolution was first tested using the paddles, however the tablets floated on the surface reducing the surface area in contact with the water and affecting the dissolution. Therefore, the dissolution was done using the paddles at a speed of 100rpm and the tablets were put inside the sinkers and dropped into the vessel.

At first, the dissolution test was done using the tablets with holes. Multiplicity of 3 tablets was used. Figure 3.18 shows the dissolution profiles. The release of the drug was immediate. The difference between the sample with no holes and the samples with holes was noticeable. For the control tablet, 80% of the drug was released within 30 minutes. By adding holes, 80% of the drug was released within 20 minutes. However, increasing the number of holes did not affect the dissolution.

Next, the dissolution test was done for the delayed release tablets. As expected, it was shown in Figure 3.19 that the outer layer of PVA can delay the release of acetaminophen. When the tablet was uncoated, acetaminophen was released immediately where 80% of it was released within 30 minutes. When the tablets were coated, release was delayed systematically by 30, 90 and 120 minutes. Our results showed that 80% of the drug was released within 200, 225 and 260 minutes for coating of 0.5, 1 and 1.5 mm, respectively. There was no exact trend to relate the thickness of PVA with the lag time observed.

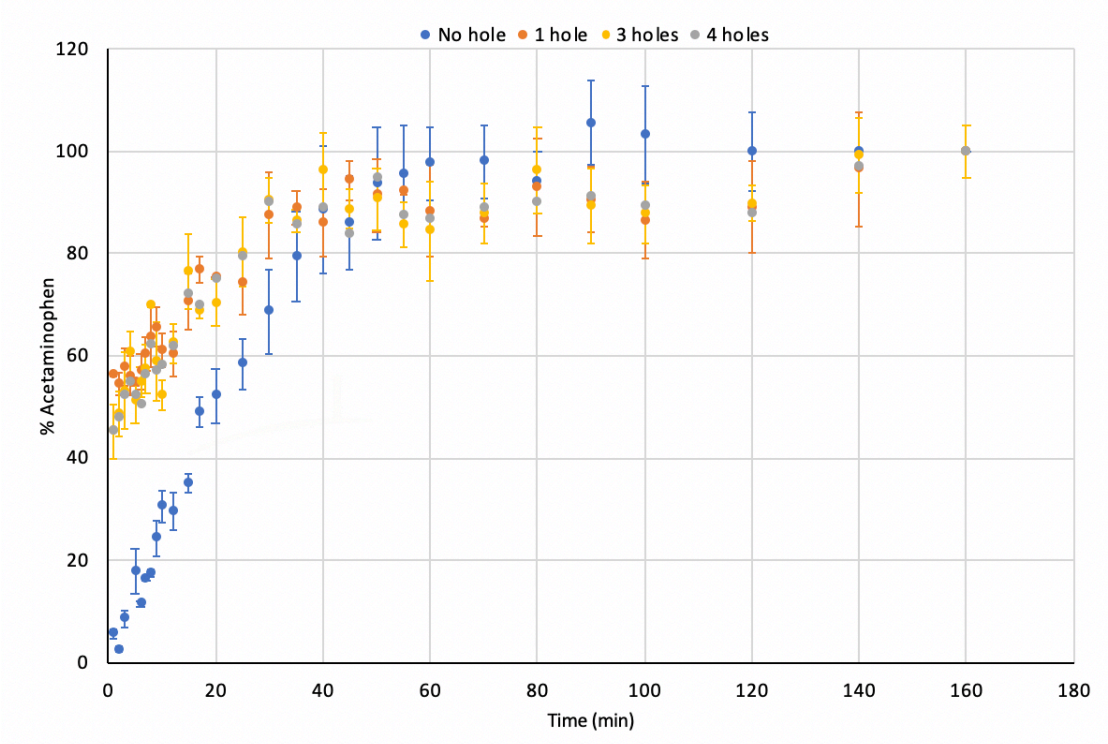


Figure 3.18 Dissolution profiles of 3D printed tablets containing acetaminophen. Tablet designs contained varying number of holes with equal final hole volume. Control tablet did not have a hole.

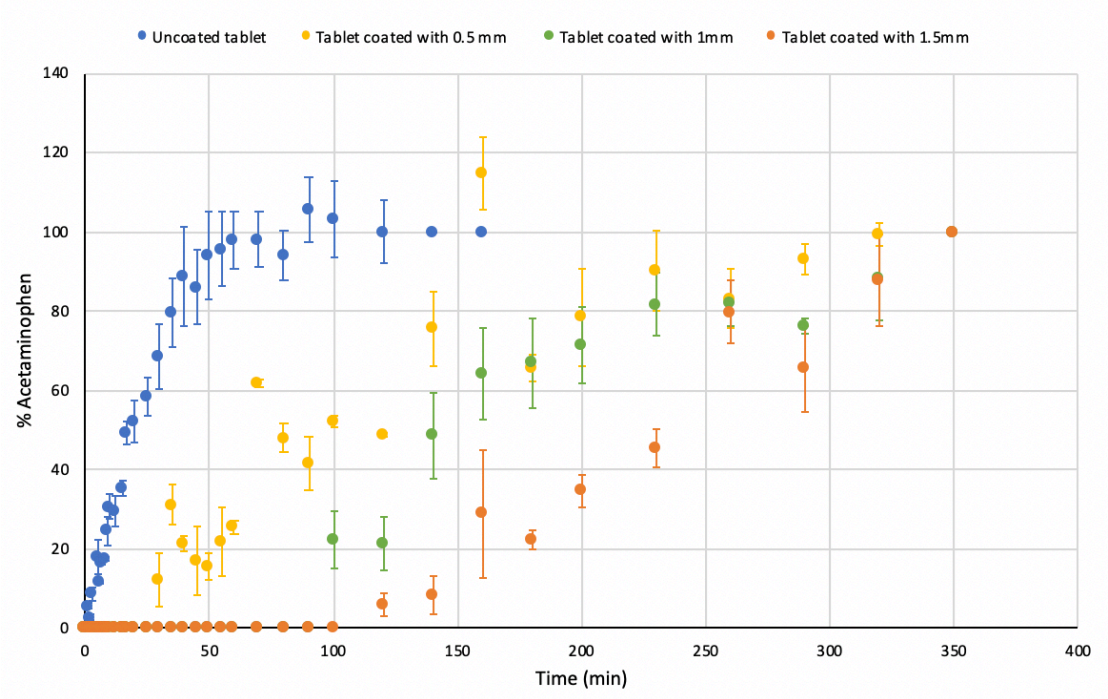


Figure 3.19 Dissolution profiles of the 3D printed PVA+ acetaminophen tablets without and with varying PVA coating for delayed release.

CHAPTER 4

CONCLUSIONS

In this study, we aim to develop 3D printed oral tablets with various designs to control the drug release time. For this purpose, we successfully fabricated PVA filaments containing acetaminophen or caffeine. In house manufactured filaments were not uniform in size and usually smaller than the commercially available filaments. Thus, we modified our 3D printer to enhance the printing performance. Print head gear coated with an elastic band enabled strong grab of the filament, and significantly enhanced printing.

Thermal analysis showed that the materials was stable throughout the process, and results helped us to determine the extrusion and printing temperatures. The filaments were successfully printed using our FDM printer. The models with holes and the models with outer PVA coating were printed, and the drug release tests showed an immediate release for all the tablets with holes. Adding more holes was not effective and it did not show any difference in release profile. For the models with coating, we showed that the PVA coating was feasible to delay the release of the drug. The thicker the coating, the longer the lag time before the release.

FDM 3D printing is a promising manufacturing method in the pharmaceutical industry to achieve different release profiles by simply changing the tablet designs. It is a simple and versatile method that can help the industry to evolve more. Further development and research are needed for this method to become feasible and used by the industry.

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