A Thesis

entitled

Formulation and In-vitro Evaluation of FDM 3D Printed Tablet with different Drug Loading

by

Farhana Noor Subah

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the

Master of Science Degree in

Pharmaceutical Science

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An Abstract of

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Patient-specific medicine is a growing area of treatment in the healthcare sector and additive manufacturing, or 3D printing technology is a recent pharmaceutical approach to confront the challenge of this individualized drug delivery system. The focus of this study was to investigate the feasibility of formulating a 3D printed personalized dosage form using fused deposition modelling (FDM) in combination with hot-melt extrusion (HME) process. Acetaminophen was selected as a model drug and a commercial polyvinyl alcohol (PVA) filament was used to fabricate 3D printed tablets with two different drug loading percentages. After screening several polyvinyl alcohols (PVA), the commercial PVA filament was selected to enhance the extrusion process. 5% and 15% acetaminophen loaded filaments were successfully extruded through a filament extruder and tablets were printed using an FDM 3D printer. Thermal analysis using DSC and TGA confirmed the thermal stability of 3D printed tablets. No endothermic events corresponding to acetaminophen were observed in the DSC thermograms of drug-loaded filaments and tablets indicating that the drug was amorphously dispersed in PVA. With TGA, the drug-loaded filaments and tablets did not show any appreciable weight loss at the printing temperature of 240 ˚C

suggesting that the polymer was stabilizing the drug. Molecular interactions of acetaminophen and PVA on drug-loaded tablets were verified through FTIR analysis. SEM micrographs of cross-sectioned drug-loaded filaments appeared to have a rough surface in compare to the commercial PVA filament due to the inclusion of acetaminophen, which was consistent with the drug-loaded tablets as well. Physical and mechanical characterization was performed according to mandated standards. The 3D printed tablets passed the weight variation, friability, thickness, dimensions, and breaking force tests with minimal outliers. Drug content loss was analyzed using a validated HPLC method. HPLC data demonstrated that increasing the temperature during the filament extrusion and FDM 3D printing process caused a measurable amount of drug loss. The prolonged disintegration time of the tablets suggested that FDM 3D printed tablets would be a considerable design for zero-order release formulation. The cylinder shape tablets exhibited higher disintegration time compared to the capsule shape with the same surface area, indicating an influence of geometrical shape on the drug release profile. The outcome of this project can mark a footprint of a revolutionary technology in the pharmaceutical industry that can facilitate the personalization of the drug delivery system.

This thesis is dedicated to my wonderful husband, Shafkat Ahmed whose unyielding love, support and encouragement enrich my soul and inspired me to pursue my research and finish it successfully. Thank you very much for having faith in me.

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Last but not the least, I want to thank my parents, my sister, Tasneem Tamanna Noor Suha and my husband for their constant support.

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List of Abbreviations

3D.....Three Dimensional

API.....Active Pharmaceutical Ingredients
ASD.....Amorphous Solid Dispersion
ATR-FTIR.....Attenuated Total Reflection - Fourier Transform Infrared Spectroscopy
AUC.....Area Under Curve

CAD.....Computer Aided Design

DLP.....Digital Light Processing
DSC.....Differential Electron Calorimetry

FDM.....Fused Diffusion Modeling
FFF.....Fused Filament Fabrication

HME.....Hot Melt Extrusion
HPLC.....High Performance Liquid Chromatography

MW.....Molecular Weight

PAM.....Pressure Assisted Micro-syringes
PVA.....Polyvinyl Alcohol

SLA.....Stereo Lithographic Printing
SLS.....Selective Laser Sintering
SEM.....Scanning Electron Microscopy

TGA.....Thermogravimetric Analysis

USP.....United States Pharmacopeia

WHO.....World Health Organization

Chapter 1

Introduction

1.1 Personalized Medication

People from different backgrounds have diversified culture, custom and metabolic system and it has created a global problem while treating individuals. Dose adjustments are now based on pragmatic methods, and that being the case, millions of unexpected side effects occur which leads to millions of deaths annually in the United States (1). Recent technologies have been optimizing treatment plans for patients based on their pharmacogenetic and pharmacokinetic profile to achieve a desired therapeutic effect and lessen the probability of adverse effect (1). Multiple therapeutic gaps including therapeutic failure, drug interactions, poor patient adherence and unacceptable treatment adherence have prevailed in conventional drug manufacturing which promoted personalization of pharmacological treatment (2). The future of drug design and therapy is most likely to convert large scale manufacturing of tablets or capsule of narrow dosing range to unpremeditated fabrication of dosage units which are personalized to patients (3). One novel strategy to face such challenges in the pharmaceutical industry is 3D printing of dosage form through which dosing strengths can be customized adjusting to individual

needs, combining multiple drugs for better patient compliance and print various geometric shapes of the oral dosage form to enhance the drug release rate (4, 5).

1.2 Tablet – Widely Used Oral Dosage Form

A tablet is a solid dosage form that consists of suitable pharmaceutical excipient and active ingredients, varies in terms of shape, size, weight, thickness, hardness, dissolution, and disintegration characteristics. There are several advantages of tablets compared to other dosage forms, such as higher stability concerning physical, chemical, and microbiological attributes, stable dose and great precision, low manufacturing and packaging cost, prolonged stability of medicaments and unpleasant taste can be masked by sugar coating. We can classify the advantages under the user or production aspect of the tablet. Most of the tablets contain five major elements – active ingredients, binder, diluent, disintegrant and lubricant (**Figure 1-1**) (6). Tablets may also contain additional ingredients such as sweeteners and/or coloring agents.

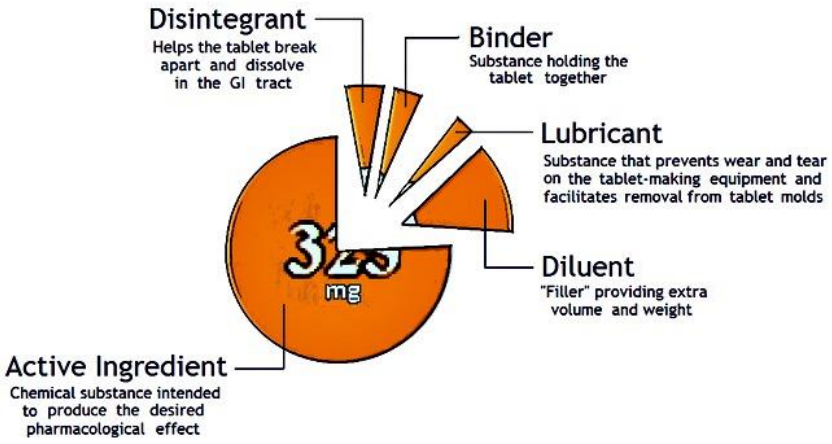

Figure 1-1: Ingredients of the tablet dosage form (6)

1.3 Conventional Tablet Manufacturing Processes

The design and manufacture of pharmaceutical tablets is a complex multi-stage process whereby formulation scientists ensure that the correct amount of drug substance in the right form is delivered at the appropriate time, at the proper rate and in the desired location with its chemical integrity protected to that point. The primary objective of the tablet manufacturing process is to formulate tablets that are:

1. Uniform in weight and drug content
2. Appropriate hardness enough to withstand mechanical shock
3. Bioavailable according to therapeutic indication requirements
4. Chemical and physical stability over a long period
5. Elegant product identity that is free from tablet defects.

Tablets are commonly manufactured by wet granulation, dry granulation, and direct compression. These methods may be considered to consist of series of steps – weighing, milling, mixing, granulation, drying, compaction, coating, and packaging. Several factors can affect the choice of the fabrication process, such as

1. Compression properties of the Active Pharmaceutical Ingredient (API)
2. Physical and chemical stability of the API during the manufacturing process
3. Particle size of the formulation ingredients/raw materials
4. Availability of the necessary processing equipment
5. Cost of the manufacturing/formulation process.

1.3.1 Wet Granulation Method

Wet granulation is a widely used method for the fabrication of compressed tablet. It is a popular method because it can be applied to any drugs with a wide range of dose percentage. It is essentially a process of particle enlargement by agglomeration involving several steps and the use of an adhesive substance known as a binder (7). In this method, APIs are mixed properly with powder excipient and binder solution after weighing and milling to form a damp mass. 6 to 12 mesh screens are used to produce pellets or granules which are dried afterwards. Higher mesh sizes such as 14 to 20 mesh screens are used to reduce the granule size. Then, the dried granules are mixed with suitable lubricants and disintegrants before compressing them into tablets, as shown in **Figure 1-2** (8). Wet granulation ensures better content uniformity, especially for soluble low-dose drugs. But this process often requires several processing steps which incur high cost on drug formulation. It is also not suitable for thermolabile and moisture-sensitive materials and there is a chance of substantial material loss due to the continuous transfer of materials from one step to another (9).

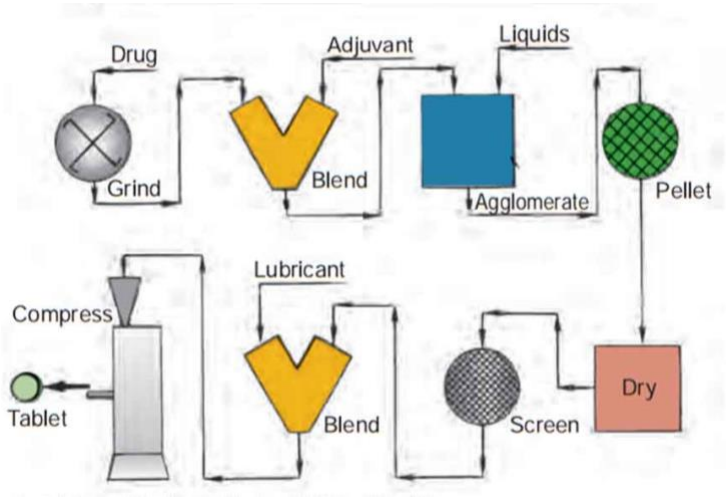

Figure 1-2: Wet granulation method for the tablet formulation (8)

1.3.2 Dry Granulation Method

Dry granulation also referred to as pre-compression or double compression, is a size enlargement process designed to improve the flow and compression characteristics of powders that would otherwise be unsuitable for compression. This method is used when tablet excipient has sufficient inherent binding properties. It can also be used as a means to avoid exposure of drug substances to elevated temperatures (during drying) or moisture. Compaction for the dry granulation process is generally achieved either by slugging or roller compaction. After milling and sieving of slugs, it is mixed with disintegrant and lubricant. In the final steps, granules are compressed into tablets, as shown in **Figure 1-3** (8). The major advantage of dry granulation over wet granulation is its lower cost due to fewer processing steps. On the contrary, a considerable amount of dust is generated during the formulation of drug-using this method. The tablets fabricated using this method tend to be softer which make them difficult for tablet coating.

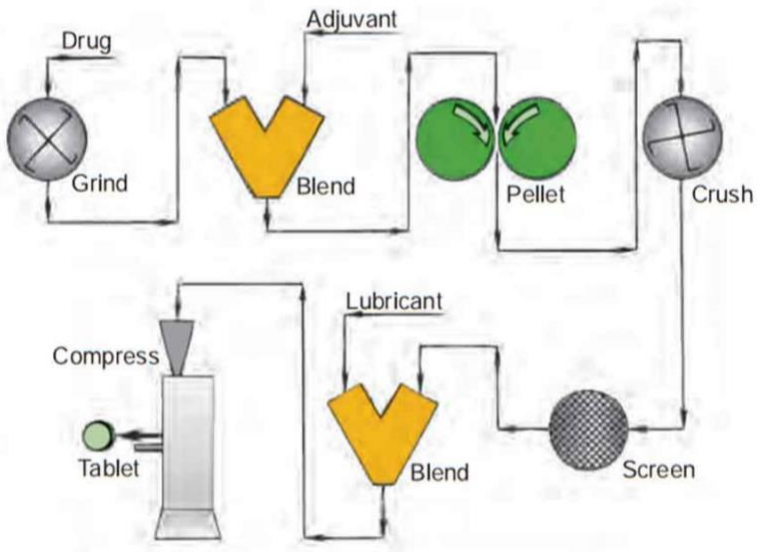

Figure 1-3: Dry granulation method for the tablet formulation (8)

1.3.3 Direct Compression Method

Direct compression is the most popular method of fabricating tablets as it is a relatively straightforward approach with the fewest manufacturing steps compared to other processes such as wet granulation and dry granulation. This method includes two primary steps: blending the APIs with excipients and compressing the finished tablets, as shown in **Figure 1-4** (10). Apart from process simplicity, the key advantages of direct compression encompass reduced capital, labor and energy cost for manufacture and the avoidance of water for granulation for water sensitive substances. However, direct compression is limited to low drug loading percentage which also may lead to non-uniform blending, unsatisfactory tablet strength and dissolution failure. Also, the excipients used in this method are often more expensive compare to the other processes.

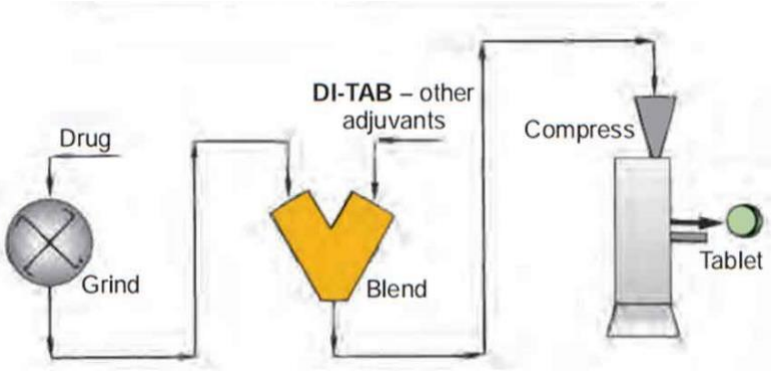

Figure 1-4: Direct compression method for tablet formulation (10)

1.4 Evolution of a Novel Drug Delivery System

The healthcare system has recently seen a movement towards personalized medicine. Ginsberg et al. defined it as medicine created from the analysis of an individual's genetic testing and molecular profile to increase the effectiveness of the prescribed treatment and minimize the adverse effect on the patient's body (11). The factors driving

this change include the development of low flow drugs with narrow therapeutic indices, the increasing awareness and importance of pharmacogenomics (for instance in the drug sensitivity of cancer sufferers) (12) and the necessity to formulate drug combinations. The aforementioned conventional large-scale pharmaceutical manufacturing processes are not suitable and cost-effective for personalized drug and also can't achieve the complexity in the dosage forms in terms of geometry, drug loading variations, distributions, and combinations. To encounter this challenge, the pharmaceutical industry has recently embraced a novel and effective manufacturing technology – 3D printing, which has the potential to tailor solid dosages based on individual's requirement at low cost.

1.5 Three-dimensional (3D) Printing

Three-dimensional (3D) printing, also referred to as additive manufacturing, is an innovative technology that uses computer-aided design (CAD) to construct objects of various materials like plastics, composites, and biomaterials by a layering method (13). The uses of 3D printing have been significantly increased since the last decade in different industries including electronics, consumer products, aerospace, motor vehicles, industrial machinery, military and healthcare sector (14-16). Though 3D printing introduced and adopted lately in the healthcare sector compare to others, it has already created an enormous opportunity for this industry. Currently, the three key applications of 3D printing in healthcare are – orthopedic implant, personalized surgery, and medical and dental devices (8). It also has the potential to disrupt and transform the manufacturing paradigm in the pharmaceutical sector by enabling on-demand fabrication of personalized drugs in the form of various dose, shape, size and release profile (17). 3D printing can revolutionize

the way oral dosage is fabricated at all stages of the drug development chronology, from pre-clinical studies and first-in-human (FIH) clinical trials to on-demand production in hospitals and pharmacies. The recent approval of SPRITAM® by the Food and Drug Administration (FDA), a levetiracetam drug manufactured by Aprecia Pharmaceutical Company (USA) for the treatment of seizures (18), has explored the use of 3D printing in the pharmaceutical sector. According to Market Data Forecast, the global healthcare 3D printing market size was worth USD 973 million in 2020 and is anticipated to grow at a compound annual growth rate (CAGR) above 18% (**Figure 1-5**) (19).

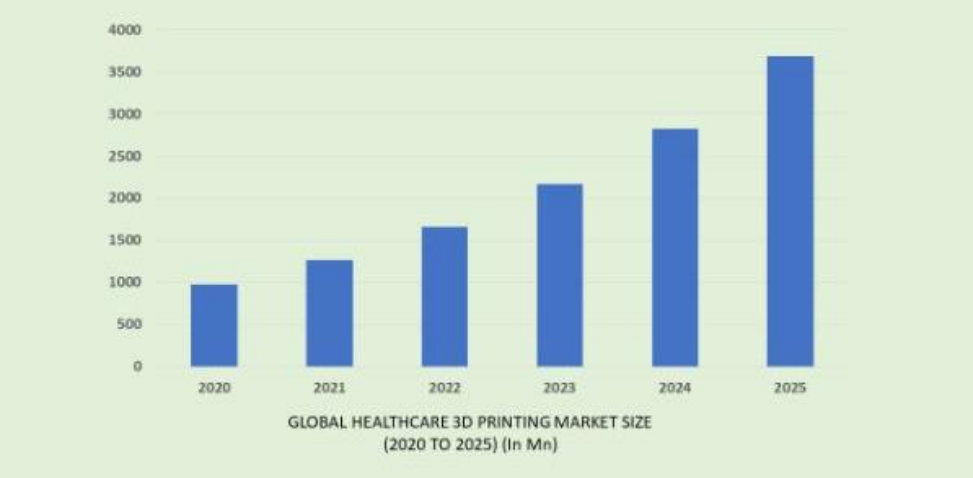

Figure 1-5: Global 3D printing market size in the healthcare sector (19)

1.5.1 Emergence of 3D Printing in Pharmaceutical Sector

3D printing technology first developed and patented at the Massachusetts Institute of Technology (MIT) by Emanuel M. Sachs et al. in 1993 (20). Various types of printing techniques have been developed over the years based on the design of formation, material selection, durability, surface finish and manufacturing speed and cost (13, 21, 22). In 1996,

Wu et al. first used the continuous inject printing technique to make drug delivery devices with complex concentration profiles (23). He demonstrated that complex drug delivery regimes can be created this way, such as the release of multiple drugs or multiphase release of a single drug. Since this work, there has been remarkable advancement of 3D printing in pharmaceuticals not only using inject printing but also other techniques as well such as FDM and SLA.

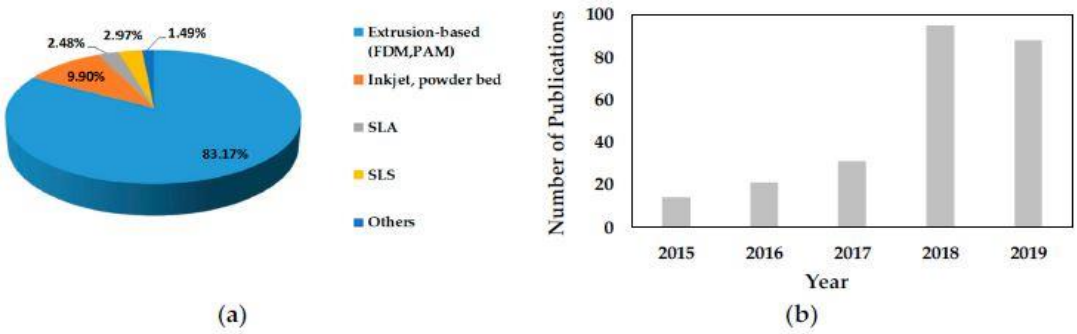

Figure 1-6: **(a)** The proportion of research articles published on different types of 3D printing processes from 2015 to 2019 (**b**) The number of published scientific articles (research and review) which reported the use of extrusion-based (FDM) or pressure-assisted micro syringe (PAM)) 3D printing (42)

The technologies used for the development of pharmaceutical drugs and delivery systems are extrusion-based printing (fused deposition modelling (FDM) (24, 25), pressure-assisted micro syringes (PAM)) (26-28), powder-based printing (powder bed and powder jetting) (29-31), selective laser sintering (SLS) printing (32, 33), stereolithographic (SLA) printing (34-36), inject printing (37, 38), and digital light processing (DLP) (39, 40). Among all these methods, extrusion-based printing (FDM and PAM) is widely accepted

by pharmaceutical researchers because of the simplicity, low cost, a wide range of usable polymers with and without drug, ability to control drug release rate by tuning geometry and polymer and ability to print at room temperature (41). Among the published articles on existing 3D printing technologies during the period 2015-2019, 83.17% used extrusion-based printing which reflects the interest and popularity of this method (**Figure 1-6**) (42).

1.5.2 Fused-diffusion Modeling (FDM) 3D Printing

Fused diffusion modelling (FDM), or Fused Filament Fabrication (FFF), is an additive manufacturing process that belongs to the material extrusion family. In this method, an extruded polymer filament is passed through a hot extruder which softens the material and deposited on a build platform in a layer-by-layer process to form the complete 3D object based on predetermined CAD design (**Figure 1-7)** (43, 44).

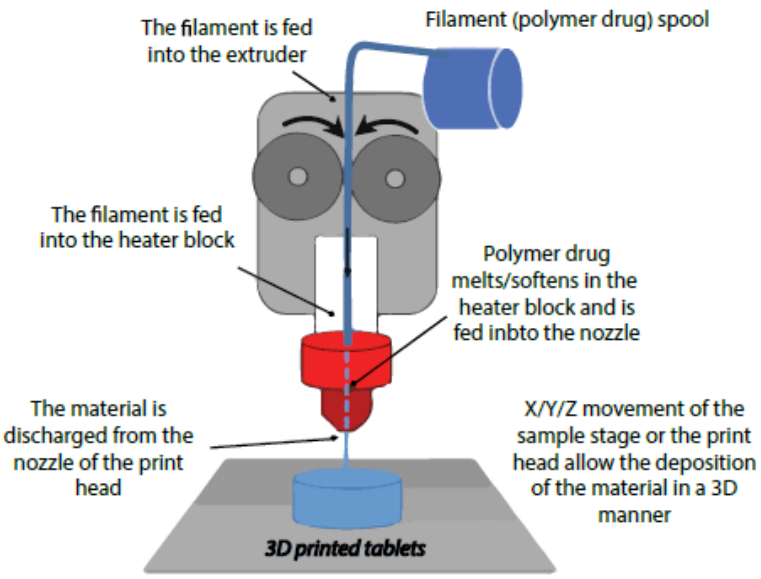

Figure 1-7: Schematic of the fused-diffusion modelling 3D printing technique (43)

Complex geometries could be fabricated by FDM 3D printers to obtain the desired shape, size, and drug release rate, which might be difficult to build using powder-based or other 3D printing technologies. FDM also offers high resolution, precision, material uniformity and good mechanical strength (2). Another prime benefit of FDM is that it's possible to blend active drug and polymer into a solid dispersion before extrusion so that the printed dosage form is drug loaded.

1.5.3 Hot Melt Extrusion (HME) Process

In FDM, a high percentage of drug loading could not be achieved as the drugs are loaded by passive diffusion from the solution. An alternative method to incorporate the drug into filament is hot-melt extrusion (HME), which is a widely recognized technique in pharmaceutical companies and academia because the industry has adapted HME for several other applications, such as amorphous solid dispersion (ASD) and melt granulation. HME is a process of applying heat and pressure to melt a polymeric mixture and forcing it with a rotating screw through an orifice in a continuous manner to produce filament, as shown in **Figure 1-8** (45). This molecular mixing converts the components into an amorphous product with a uniform shape and density, thereby increasing the dissolution profile of the poorly water-soluble drug. This exciting yet challenging technology may offer several advantages over conventional pharmaceutical manufacturing processes and more efficient time to achieve the final product. However, the limiting factors of this technology for the development of pharmaceutical dosage forms is the relative lack of the pharmaceutically acceptable polymers that can be used for the FDM 3D printing and inability to use thermally labile active ingredients.

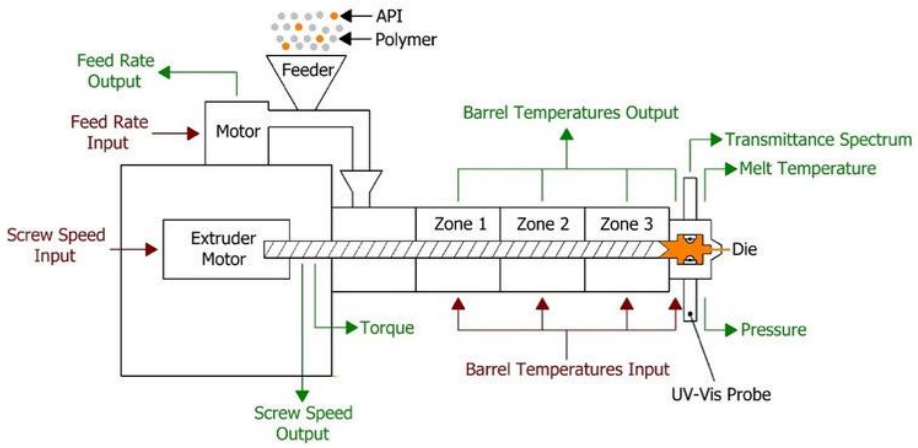

Figure 1-8: Schematic of the holt-melt extrusion process of API and polymer mixture (45)

1.6 Acetaminophen – As a Model Drug

Acetaminophen, also known as Paracetamol, is now the most commonly used drug worldwide, available ubiquitously in both prescription and over the counter, used for almost all ages and forming step 1 of the WHO analgesic ladder. First-line treatment for pain and pyrexia plays a significant role in multimodal analgesia and considered to possess a great safety profile except in significant overdose, with few drug interactions (46, 47). It was first synthesized in 1878 by Morse and introduced for medical usage by Von Mering in 1893, though it was limitedly used for more than 60 years due to concerns about acetaminophen-induced methemoglobinemia (48). Subsequently, different research groups disproved the toxicity theory and acetaminophen was released in the USA in 1950 (49-51). It is now used ubiquitously in both prescription and over-the-counter formulations with over 200 million prescriptions annually in the USA, and non-prescription sales surpassing 25 thousand million doses per year, making it the most commonly dispensed pharmaceutical in the USA (52). Acetaminophen is available in different forms including

tablets or caplets, capsules, soluble tablets, suppositories, suspensions, and liquids – usually for children. In 3D printing, the properties of the filament such as elasticity and brittleness, are practically dependent on the choice of drug that has to be blended. Acetaminophen is a BCS class I drug which has several polymorphic and amorphous form with a glass transition temperature of 23 °C (53). Having all these criteria, acetaminophen is a viable candidate as a model drug to monitor the polymorphic transition due to processing and also makes it easy to assay the effect of PVA as a drug carrier when exposed to different temperatures (54).

1.7 Selection of Polymer

Former studies have reported using different polymers such as hydroxypropyl cellulose (55), methacrylic polymers (56), polyurethane (57), hydroxypropyl methylcellulose acetate succinate (57) and polyvinyl alcohol (PVA) (58, 59) to enhance dissolution rate and achieve complete drug release profile from 3D printed tablets. Poly (vinyl alcohol) (PVA), a water-soluble, semi-crystalline, hygroscopic polymer, has been widely used for the fabrication of pharmaceutical tablets, transdermal patches, ophthalmic devices, and implants (60). Due to good thermal stability (melting point ~185˚C and temperature of degradation above 250˚C) and ability to stabilize amorphous solid dispersions (ASD), PVA is a promising candidate to be studied in both FDM printing and HME. Despite being a suitable polymer candidate, the use of plasticizers must be considered to decrease the brittleness of the filament and increased porosity (58, 59).

Chapter 2

Aim of Study

1. To investigate the processability of acetaminophen with different drug loading percentage (5% and 15% w/w) using fused diffusion modelling (FDM) 3D printing technology after the polyvinyl alcohol (PVA) based filament extruded through hot-melt extrusion (HME) process. Here, acetaminophen was selected as a model drug as it is widely available and suitable for a proof-of-concept study.

2. To prepare 3D printed tablets of cylinder and capsule shapes of the trial formulation. These two shapes were chosen for printing tablets.

3. To evaluate the *in-vitro* drug release of acetaminophen from drug loaded PVA filaments, and 3D printed tablets of cylindrical and capsule shapes. The same shape was selected to compare between the fabrication process and characteristics of 5% and 15% drug-loaded tablets, whereas different shape with same drug load percentage (15%) was chosen to analyze the effect of geometrical shape on drug release profile. Both the drug-loaded filaments and tablets were evaluated *in-vitro* and physical, mechanical characterization was performed on the 3D printed tablets.

Hence, the viability of fabricating personalized drug, using the FDM 3D printing process and the effects of drug loading percentage were the main concern of this study.

Chapter 3

Materials and Methodology

3.1 Materials

In this study, two major materials were used to fabricate FDM 3D printed tablet – PVA and acetaminophen.

PVA is a colorless, water-soluble synthetic polymer. It has the chemical formula $[CH_2CH(OH)]_n$. Recently, PVA-based polymers are being widely used as binder substance to manufacture 3D printed oral dosage forms with modified drug release profile. Three different grades of PVA were used in this study. Solid powder of polyvinyl alcohol (87.0 - 89.0 % hydrolyzed; M.W. approx. 13,000 – 23,000 g/mol) and microcrystalline powdered polyvinyl alcohol (88% hydrolyzed; average M.W. 20,000 – 30,000 g/mol) were purchased from Fisher Scientific, USA. Another commercial PVA filament roll was purchased from Matterhackers.com (CA, USA).

Acetaminophen is an analgesic used to temporarily relieve minor aches and pains due to headache, muscular aches, backache, minor pain of arthritis, the common cold, fever, toothache, and premenstrual and menstrual cramps. Its chemical formula is $C_8H_9NO_2$ and molecular weight 151.16. It is available under different brand names. For this study,

white crystalline fine powder acetaminophen USP was bought from PCCA, TX, USA. It is slightly soluble in cold water and more soluble in hot water, alcohol and acetone. It has a melting temperature of 168 to 172 °C (61).

All other materials used were of analytical grade and used as received. **Figure 3-1** shows the chemical structure of PVA and acetaminophen.

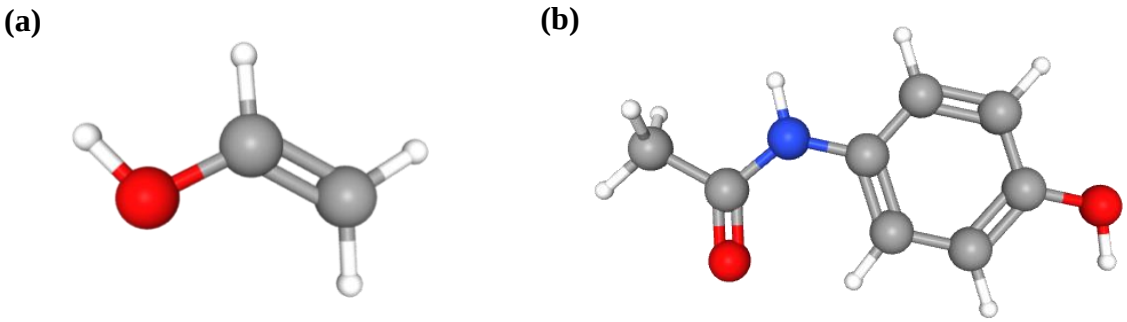

Figure-3.1: Chemical structure of (a) PVA and (b) Acetaminophen

3.2 Methodology

3.2.1 Preparation of filaments by HME

Filaments with neat PVA and PVA-acetaminophen mixture was extruded using a 3DEVO filament extruder (Netherland, EU) through hot-melt extrusion (HME) process. At first, the powdered form of PVA with two different molecular weights was tried for 3D printing but the extruded filament with these materials was too brittle and not ideal for 3D printing (**Figure 3-2**). Later, commercial PVA filaments with different molecular weights were chosen for FDM 3D printed tablets since the extrusion result was of good quality and the molecular weight of the commercial PVA filament was found to be 3000 g/mol. For extruding the drug-loaded filaments, at first, the commercial filament was chopped with a

filament pelletizer and crushed using liquid nitrogen with a small high-speed liquid nitrogen pulverizer. They were kept in a dryer (JEIO Tech Oven, Korea) at 85 °C for drying overnight and Acetaminophen powder was kept separately at another dryer (PrintDry™, USA) at 45 °C overnight so that no moisture is present. The next day, just before processing the filaments, the crushed PVA powder and acetaminophen were weighed and homogenously mixed at a weight ratio of 95:5 and 85:15 accordingly. The physical mixture of PVA and acetaminophen was blended using a mortar and pestle for 5 minutes and put into the extruder in small quantities in succession. The drug-loaded filaments were extruded at 195 °C through a steel extruder nozzle at 5 rpm and an average diameter of 1.7 mm of the filament was collected through the diameter sensor of the machine. The extrusion process was started at 180 °C and the final extrusion temperature was 195 °C; constant for both the drug-loaded filaments. The extruded filaments were protected from light and kept in the dryer (JEIO Tech Oven, Korea) at 75 °C until printing.

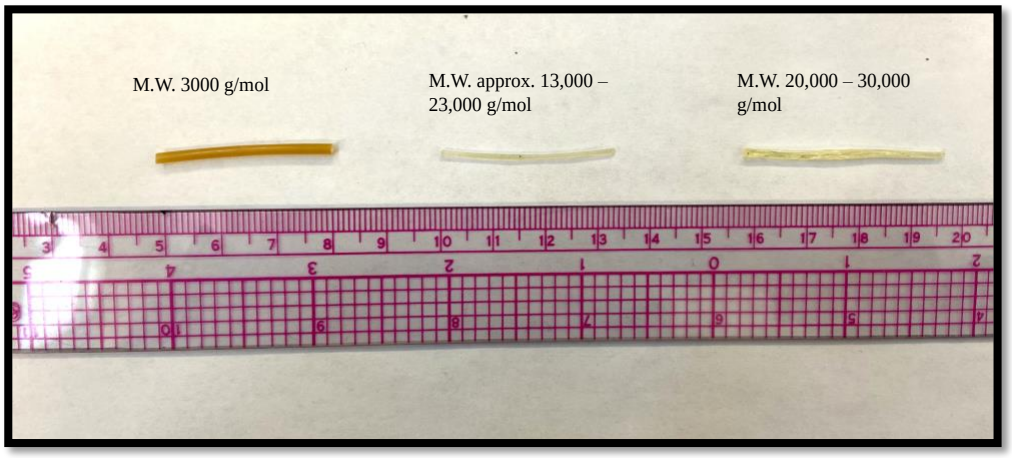

Figure 3-2: Image of extruded filaments using different molecular weights of PVA

3.2.2 Designing of Tablets

Two different shapes were chosen for FDM 3D printed tablets. One was cylinder shaped and the other was capsule shaped (**Figure 3-3**). Cylinder shape was used to analyze the difference of 5% and 15% drug loaded tablet's manufacturing processes and properties. The capsule shape with the same surface area as the cylinder shape was fabricated to compare the effect of geometry on drug release profile. The templates for printing the tablets were designed with Solidworks® (Dassault Systèmes SolidWorks Corporation, USA) and exported as stereolithography (.stl) file. The surface area of both shapes was kept constant at 314 mm^2 with an infill percentage of 100% and their lengths, width and diameter were drawn accordingly. The dimensions of both shapes are shared in **Table 3.1**. A raft was designed to increase the adherence of the printed tablets to the hot glass plate of the 3D printer. It kept the tablets balanced during printing (62). The raft was easily taken off without ruining the printed tablets.

(a) **(b)**

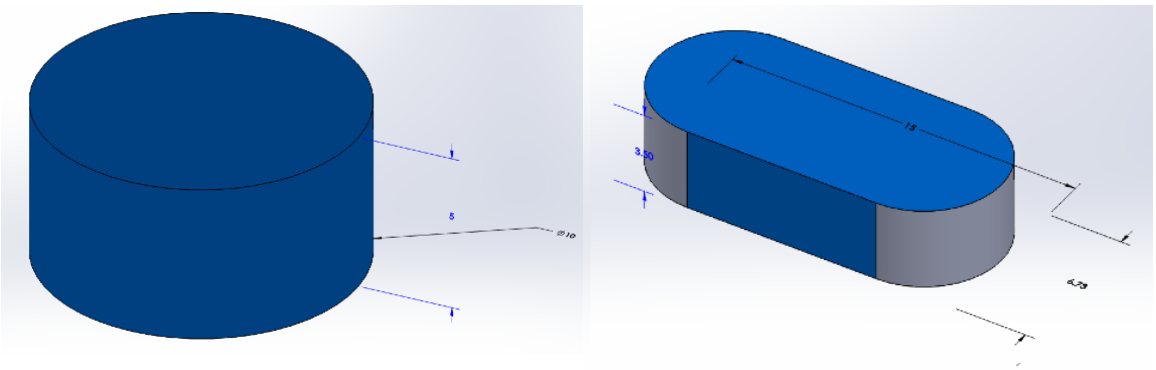

Figure 3-3: Solidworks® design of 3D printed tablets (a) Cylinder shape and (b) capsule shape

Table 3.1: Dimensions of the 3D printed tablets on Solidworks® design

Shapes of Tablets	Dimensions in Solidworks®
Cylinder	Diameter = 10 mm Thickness = 5 mm
Capsule	Length = 15 mm Width = 6.73 mm Thickness = 3.5 mm

3.2.3 Fabrication of 3D Printed Tablets using FDM

The tablets were fabricated with drug-loaded filaments using a FDM 3D printer (AON 3D, Montreal, Canada). The 3D printer bed temperature was kept constant at 70 °C and the height of each printed layer was kept at 0.2 mm. The printing was performed at a nozzle temperature of 240 °C with a 0.4-mm brass nozzle at 25 mm per second printing speed.

3.2.4 Characterization of Filaments and Tablets

3.2.4.1 Images of Filaments and Tablets

The images of filaments and 3D printed tablets were taken with a high-resolution digital camera of a cellphone.

3.2.4.2 Scanning Electron Microscopy (SEM)

Morphology of cross-section of the filaments, the surface of 3D printed tablets and pure acetaminophen powder were examined by using Hitachi S-4800 High-Resolution Scanning Electron Microscope (Hitachi High-Technologies Corp., Tokyo, Japan). The samples were fixed on an aluminum stub using a double-sided carbon tape and made electrically conductive by sputter coating (Cressington 108 auto Sputter Coater, Watford, UK) with a thin layer of gold for 10 seconds. The images were obtained at an acceleration voltage of 5.0 kV and magnification of 500x and 800x.

3.2.4.3 Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed on pure acetaminophen, PVA, 5% drug-loaded filament and tablet and 15% drug-loaded filament and tablet using DSC 250 analyzer (TA Instruments, DE, USA) to determine and compare their melting point at the mixed state and observe any changes in the physical state due to heat. Approximately 8 mg of each sample was weighed on a tared T-zero® aluminum pan and enclosed with a hermetic lid. All the samples were equilibrated at -20 °C and heated up to 250 °C at a heating rate of 10 °C/min under 50 ml/min nitrogen flow. An empty sealed T-zero® aluminum pan was used as a reference. Two heating cycles were run to closely monitor the glass transition temperatures (Tg) of the samples. After the second heating cycle, the samples were cooled to 40 °C.

3.2.4.4 Thermogravimetric Analysis (TGA)

Thermogravimetric analysis (TGA) was performed on pure acetaminophen, PVA, 5% drug-loaded filament, 15% drug-loaded filament, 5% drug loaded tablet and 15% drug loaded tablet to determine the percentage weight loss due to heat in filament extrusion process and 3D printing. Similar to DSC, TGA indicates the thermal stability of the test materials. TGA Q50 (TA Instruments, New Castle, DE) was used to run the test which was calibrated under nitrogen purge (40ml/min). Approximately 18 mg of each sample was weighed onto a tared platinum pan. The heating rate was maintained constant at 10 °C/min and heated up to 600 °C for all the samples.

3.2.4.5 Attenuated Total Reflection - Fourier Transform Infrared Spectroscopy (ATR-FTIR)

ATR - FTIR analysis was conducted to analyze the intermolecular interaction between pure acetaminophen, PVA, 5% drug loaded tablet and 15% drug loaded tablet. Infrared spectra were obtained using a Micro ATR-FTIR (Digilab UMA 600, Hopkinton, MA). The resolution was established at 3.32 cm^{-1}; transmittance was more than 99% for all the samples. 256 scan numbers were chosen to obtain good FTIR spectra. All the obtained spectrums were analyzed using Resolutions pro software (Agilent Technologies, Mulgrave, VIC).

3.2.4.6 Weight Variation Test of 3D Printed Tablets

10 tablets from each batch – 5% drug-loaded, 15% drug-loaded cylinder shape and 15% drug-loaded capsule shape were randomly chosen. They were individually weighed on a digital balance (Mettler Toledo, USA). The average of the weights and the individual percentage deviation were calculated according to USP <905> Uniformity of Dosage Units (63).

3.2.4.7 Thickness of 3D Printed Tablets

Pre-weighed 3 tablets from each batch – 5% drug-loaded, 15 % drug-loaded cylinder shapes and 15% drug-loaded capsule-shaped tablets were selected to test the tablet thickness. A digital slide caliper (Vinca® DCLA) was used to take the measurements, the average thickness and the standard deviation is reported.

3.2.4.8 Friability of 3D Printed Tablets

A friability test, according to USP <1216> Tablet Friability (64), was performed to determine the tablets resistance to chipping, capping and abrasion that occur while manufacturing, processing and shipping processes. 10 tablets from each formulation – 5% drug-loaded, 15% drug-loaded cylinder-shaped and 15% drug-loaded capsule-shaped were initially weighed and measured their friability in a Roche type friabilator (Erweka, Germany). Rotation speed was maintained at 25 rpm for 10 min. The tablets were re-weighed after the test and their friability was calculated using **Equation 3.1** –

$$\text{Friability (\%)} = W_1 - W_2 / W_1 * 100 \quad (3.1)$$

Where,

W_1 = Initial weight of the tablets before test

W_2 = Final weight of the tablets after test

3.2.4.9 Breaking Force Test of 3D Printed Tablets

According to the USP <1217> Tablet Breaking Force (65), a tablet breaking force test is performed to measure the crushing strength and structural robustness of tablets. Three FDM 3D printed pre-weighed tablets with similar thickness were randomly chosen from each batch – 5% drug-loaded, 15% drug-loaded cylinder-shaped and 15% drug-loaded capsule-shaped. They were examined for breaking force test using an apparatus (type H1 T, Sotax, MA, USA). The average breaking force and standard deviation were calculated.

3.2.4.10 *In-vitro* Disintegration Test of 3D Printed Tablets

The *in-vitro* disintegration test was carried out as per USP <701> Disintegration (66) on three randomly chosen pre-weighed tablets. The tablets were put in each basket – rack of the disintegration apparatus (Erweka, Germany) and immersed in 1000 mL filtered distilled water. The temperature of the water was maintained at 37 ± 5 °C. The time for complete disintegration was recorded. The average disintegration time and the standard

deviation is calculated and reported. A single factor or one – way ANOVA test was done to test the null hypothesis that the means of tablet disintegration times are all equal.

3.2.4.11 Quantifying Drug Content using HPLC

Acetaminophen from FDM 3D printed 5% drug-loaded and 15% drug loaded tablets were quantified using High-Performance Liquid Chromatography (HPLC) method. Chromatography was performed on an HPLC (Waters e2695 Separation Module, Milford, MA) equipped with a BDS Hypersil C18 reversed-phase column (150 x 4.6 mm, Particle size 5 micron) and for detection, a Photodiode Array (Waters 2998, MA, USA) was used. The column temperature was set at 40 °C. The mobile phase consisted of 15% methanol and 85% filtered distilled water. This mobile phase content was also used as sample dilution media. The pump flow rate was set up at 1 ml/min. The injection volume was 20 µl and the detection was carried out at 247 nm. The run time was set up for 6 minutes. Data were collected using EMPOWER software (Waters, MA, USA). Different calibration standards of pure acetaminophen were prepared in the same mobile phase media and the retention time was found at 4.5 minutes. For the calibration curve, each standard was analyzed in triplicate and the average Area Under Curve (AUC) peak was plotted against concentration. The assay method was found to be linear with a correlation coefficient of 1. The drug content was quantified by plotting into the calibration curve.

An average of 0.3g of both 5% and 15% drug-loaded filaments and 0.4 g of both 5% and 15% drug loaded tablets were dissolved in 1L of filtered distilled water. It took approximately 1 hour for the filaments to dissolve, and the tablets took approximately 5

hours to dissolve with magnetic stirring at 90 rpm (Fisher Scientific, Waltham, MA). 5 ml of sample was collected, and micro-filtered using polyvinylidene fluoride (PVDF) 0.2 µm (Fisher Scientific, Walthan, MA) syringe filter. 100 µl from the filtered solution was pipetted to an Eppendorf tube (1.5 µl, FisherBrand®) which was then diluted with 100 µl of the dilution media (15% Methanol + 85% filtered DI water). The diluted solution was then mixed with a vortex mixture (Fixed speed vortex mixture, Fisher Scientific, Waltham, MA). 100 µl was pipetted from the solution to the HPLC vial (Phenomenex®, Torrance, CA).

Chapter 4

Results and Discussion

4.1 Extrusion of Drug Loaded Filaments

Filaments with two different drug loading percentage were successfully extruded. Their diameter was maintained constant via the extrusion machine sensor and the surface was found to be smooth. The color of the commercial PVA filament was light yellow which started to change to deep yellow and brown as the percentage of drug loading was increased, as shown in **Figure 4-1(a)**. It is also assumed that, because of moisture, 15% drug-loaded filament turned to brown color.

4.2 Fabrication of 3D Printed Tablets

It was possible to fabricate three different types of tablets by FDM 3D printing with drug-loaded filaments. 5% cylinder-shaped, 15% cylinder-shaped and 15% capsule-shaped were successfully printed following the outlined method. Images are shown in **Figure 4-1(b)**. The color of the tablets was also consistent with the color of the filaments. The surface of the tablets was smooth and free of defects. Three printed tablets were randomly chosen

from two different shapes. Their dimensions were measured with a digital slide caliper (Vinca® DCLA) and compared to the theoretical dimensions of tablets designed in Solidworks® (**Table 4.1)**. The dimensions of the 3D printed tablets were comparable to the design measurements. Slightly increased dimension than the Solidworks® design was found, although a noticeable change was observed in the width of capsule-shaped tablets. Deformation in 3D printed objects occur while 3D printing due to temperature fluctuation; so small variations in dimensions are reported to be common in 3D printing (67).

(a) **(b)**

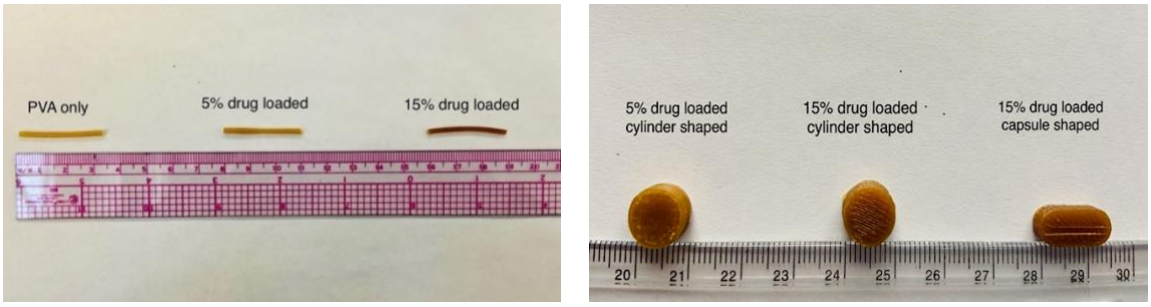

Figure 4-1: Images of (a) Drug loaded filaments compared to commercial PVA filament (b) 3D printed tablets of two different shapes with 5% and 15% drug loading percentages

Table 4.1: Dimensions of theoretical shape of tablets and 3D printed tablets

Shapes of Tablets	**Dimensions in Solidworks®**	**Dimensions of 3DPrinted Tablets (Average ± SD)**
Cylinder	Diameter = 10 mm	Diameter = 10.09 ± 0.04 mm
Capsule	Length = 15 mm Width = 6.73 mm	Length = 15.17 ± 0.005 mm Width = 7.06 ± 0.015 mm

4.3 Surface Morphology using SEM

SEM micrographs of pure acetaminophen powder, a cross-section of PVA filament, 5% drug-loaded filament and tablet, 15% drug-loaded filament and tablet are shown in **Figure 4-2 and Figure 4-3.** The sample was charging as the electron beam was passing through the pure acetaminophen powder. A cross-section of the commercial PVA filament showed smoother images than the cross-sections of the drug-loaded filaments. The surface of the filament and tablet showed the presence of roughness with the increase in drug loading percentage. Though the percentage of the drug was very low, a rough, abrupted structure for 5% filament and tablet were observed due to the incorporation of acetaminophen into PVA. Non-uniform dispersion of the drug into PVA was potentially the reason of surface roughness (68). TGA analysis and HPLC content analysis confirmed that acetaminophen was degrading during the extrusion and the printing process. This can contribute to the surface roughness. The roughness was more prominent and visible at high magnification (x800) compared to the low magnification setup (x500), which is understandable. The inclusion of a high quantity of acetaminophen can disrupt the PVA orientation in the matrix and increases the surface roughness (68). Numerous pores were observed throughout the 15% drug-loaded filament and tablet. This structural defect is commonly seen in FDM 3D printing. Recent studies have evaluated the contribution of various parameters such as viscosity, extrusion and printing velocity, and pressure on the presence of structural defects and perforating pores (69). Studies have demonstrated that the parameter “extrusion multiplier” to be strongly associated with the prevalence of porosity in FDM products. In addition to this PVA has strong vapor sorption property and

as the material passes through hot parts of the equipment the expanding moisture can leave the matrix giving it a bubbled and porous structure.

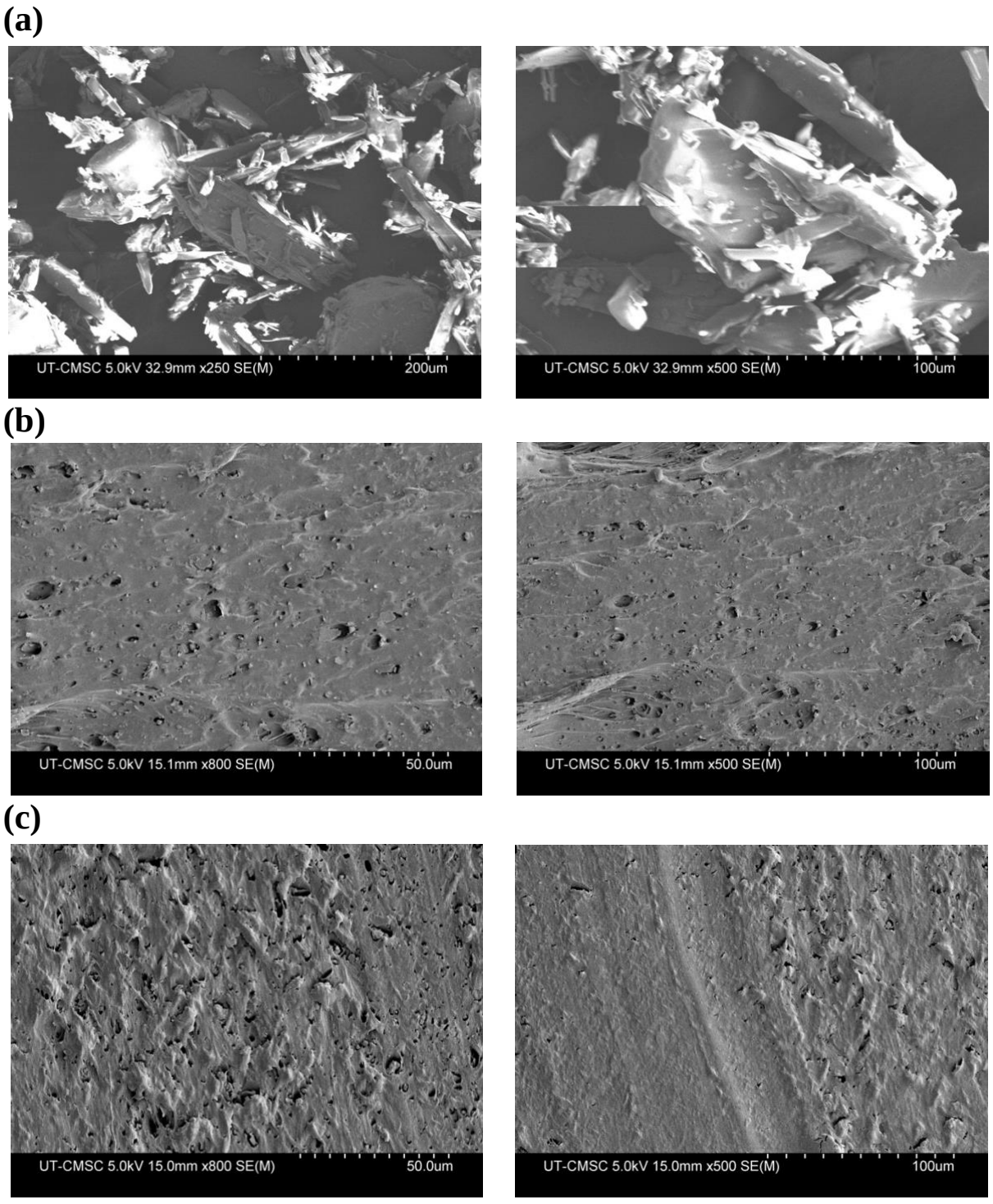

Figure 4-2: SEM micrographs at two different magnification factors – left column x800 and right column x500 of (a) pure acetaminophen powder, (b) cross-section of PVA filament, (c) cross-section of 5% drug loaded filament.

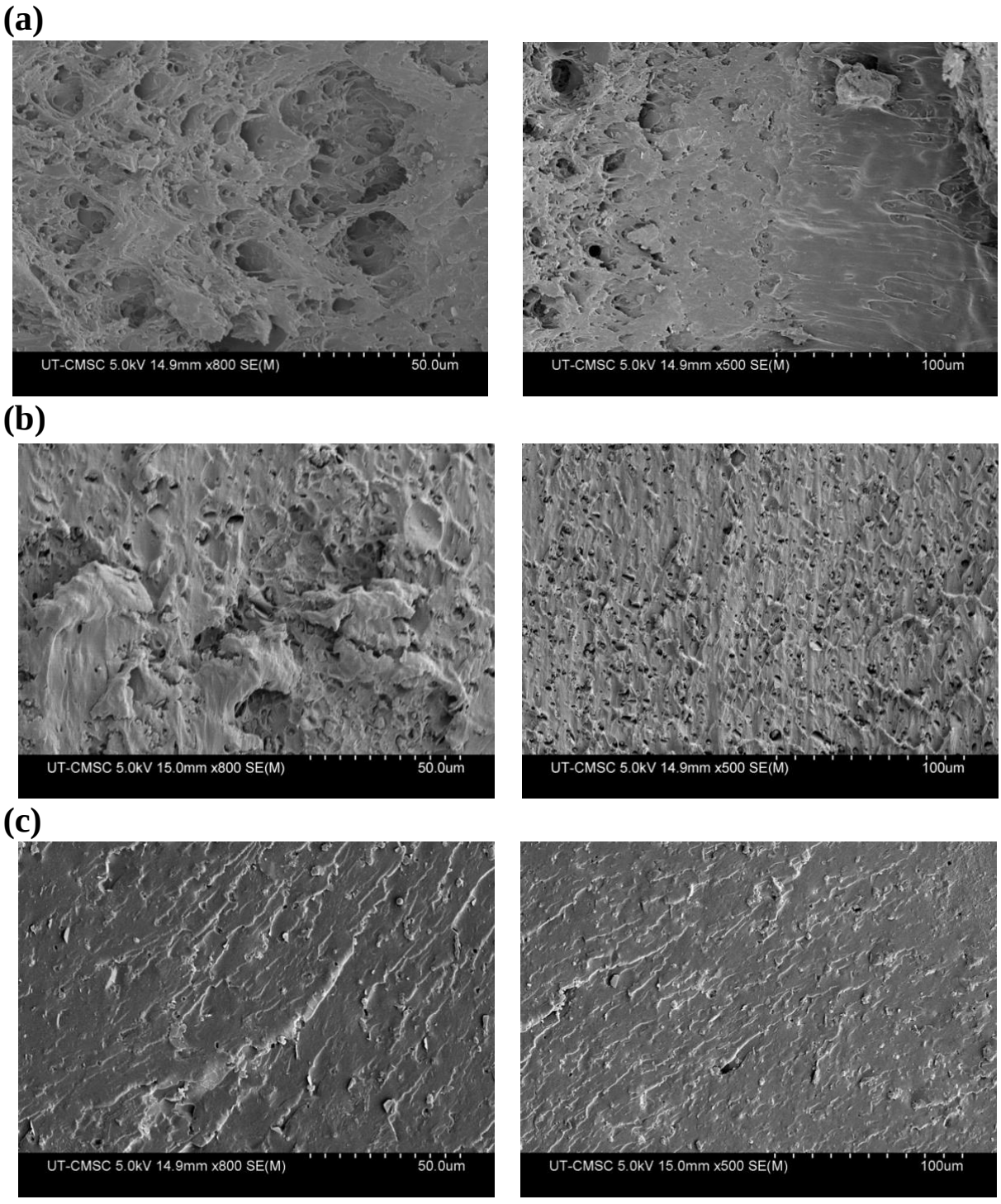

Figure 4-3: SEM micrographs at two different magnification factors – left column x800 and right column x500 of (a) cross-section of 5% drug loaded tablet, (b) cross-section of 15% drug loaded filament, (c) cross-section of 15% drug loaded tablet

4.4 DSC Analysis

The DSC data were analyzed using TRIOS software (TA Instruments, New Castle, DE) and heat flow was plotted against temperature for each sample as shown in **Figure 4-4**. Pure acetaminophen exhibited a sharp endothermic peak at 171 °C, corresponding to the melting of the drug. It also indicates that this acetaminophen USP was of acetaminophen polymorph I. In the case of PVA and PVA-containing material, the first DSC heat scan is used to remove residual solvents and thermal history of the polymer so here the 2nd DSC heat scans were analyzed for distinct glass transition temperature of the polymer containing samples (60). No significant changes in shifts were observed in endothermic peaks of the 2nd heating scan (**Figure 4-5)**. PVA melted around 191 °C and showed glass transition temperature around 60 °C indicating its semi-crystalline nature (26). This high melting point indicates that the PVA is stiff and not extrudable until it melts and keeping that in mind, the filaments were extruded at 195 °C. 5% drug-loaded filament and tablet melted around 185 °C and 15% drug-loaded filament and tablet melted around 180 °C; both are higher than 171 °C. This suggests that the drug is molecularly dispersed within the polymer matrix as a solid solution. Also melting range of 15% drug loaded samples was lower than the melting range of 5% drug loaded samples. This is possibly due to the molecular interaction between the polymer and acetaminophen. The stable temperature of acetaminophen and PVA was found similar to the TGA analysis. A glass transition temperature was observed around 60 °C for both the drug-loaded filaments which shifted to 65 °C in the drug-loaded tablets. It is suspected due to the crystalline nature of acetaminophen and multiple extrusion temperature changes of drug loaded PVA samples. The phase transition temperature (around 120 °C) of all the PVA containing samples

remained the same (**Figure 4-5**). This suggests that acetaminophen is not exerting any plasticizing effect (3). The DSC thermogram of acetaminophen after incorporating with the polymer through blending, extruding and printing exhibited significantly lower intensity endothermic peak in comparison to the peak obtained from the pure acetaminophen powder. There may be two possible explanations for this phenomenon. Acetaminophen is undergoing considerable degradation as it is extruded, and 3D printed. It is also possible that the remaining drug in the polymer matrix is less crystalline in nature and possibly molecularly dispersed in the PVA matrix (70).

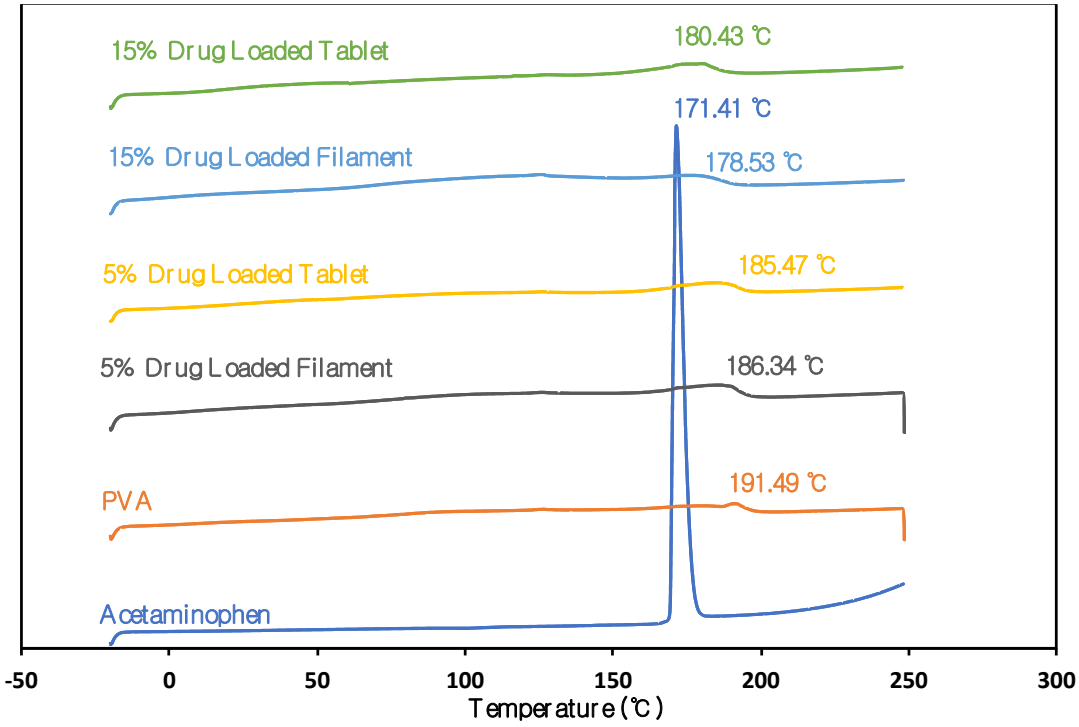

Figure 4-4: Overlay of DSC thermographs of pure acetaminophen, commercial PVA filament, 5% drug-loaded filament and tablet, 15% drug-loaded filament and tablet

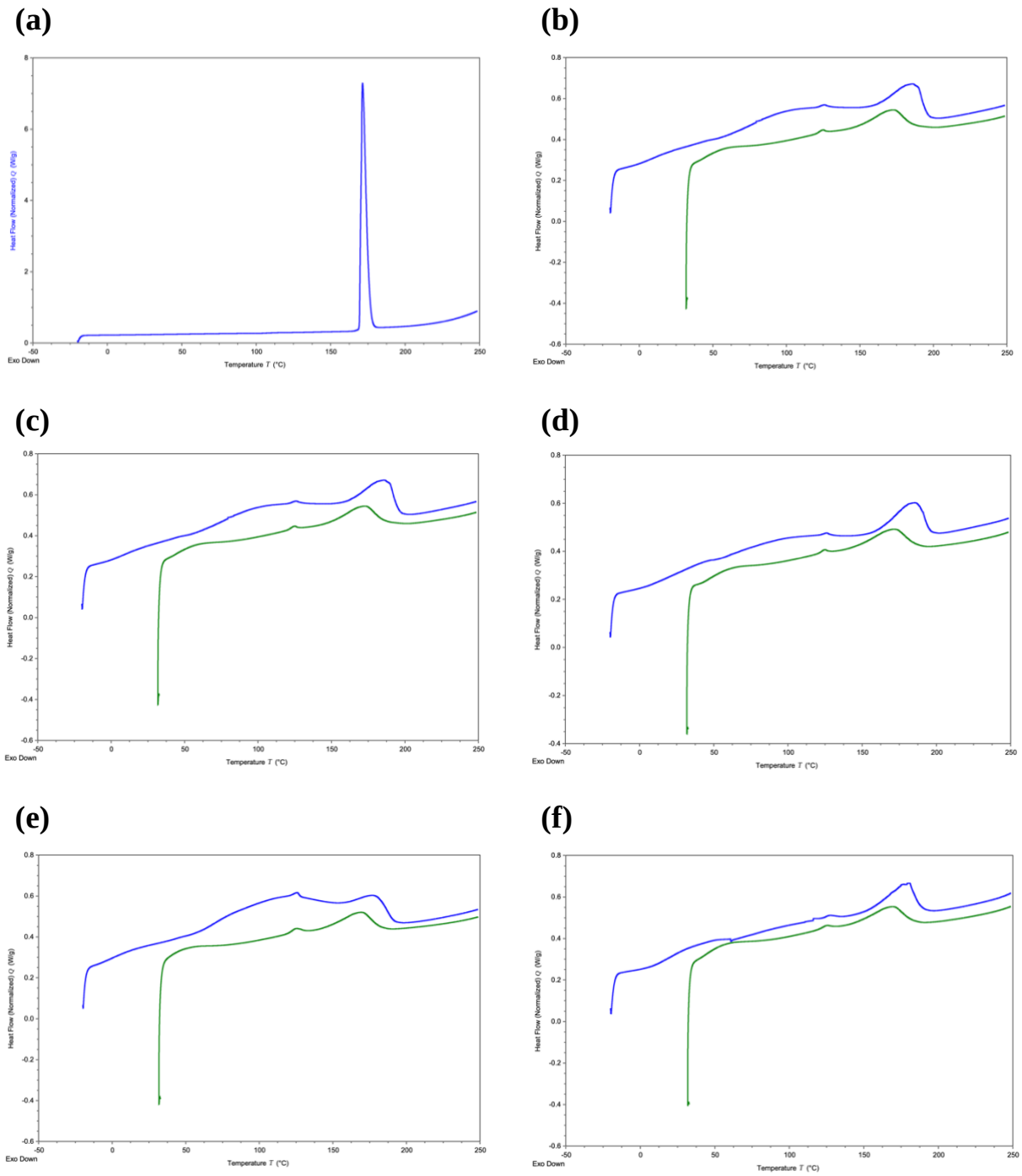

Figure 4-5: DSC thermographs of (a) pure acetaminophen, (b) commercial PVA filament, (c) 5% drug loaded filament, (d) 5% drug loaded tablet, (e)15% drug loaded filament, (f) 15% drug loaded tablet.

4.5 TGA Analysis

The TGA data were analyzed using the software TA Universal Analysis 2000 (New Castle, DE) and weight loss was plotted against temperature at a constant ramp rate of 10 °C/min. In pure acetaminophen, no significant weight loss was observed until 200 °C but weight loss occurred at temperature above 200 °C, as shown in **Figure 4-6** (26). In contrast, by 195 °C, pure acetaminophen lost 3% weight, but severe degradation occurs around 260 °C. By 195 °C PVA lost 5% weight, both the filaments lost 3% and both the tablets lost near to 4% weight. A considerable weight loss percentage was noted at the temperature at which the filaments were extruded. PVA is stable until 200 °C and pure acetaminophen is stable up to 175 °C which is consistent with the DSC results. Pure acetaminophen starts to degrade significantly above 200 °C while the drug-loaded filaments and tablets degrade significantly above 250 °C (**Figure 4-6**). The weight loss demonstrated by the PVA containing samples before 200 °C is most likely due to moisture evaporation (71). Severe degradation of all the PVA-containing materials occurs around 320 – 330 °C, as shown in **Figure 4-7**. Because of some processing challenges, the tablets could not be printed at a temperature less than 240 °C. At 240 °C, acetaminophen lost near to 30% of weight and PVA lost 8% weight, the filaments lost 4%, and the tablets lost 9% of their weight. This considerable weight loss between the drug and the drug loaded filaments as well as between the drug and the tablets supports the notion that the polymer can shield the API from thermal degradation to a limited extent (3). **Figure 4-7 (c)–(f)** shows that the major weight loss of 15% drug loaded tablet was observed at 312 °C and for 15% drug-loaded filament it was at 327 °C; both of which were less than that observed with 5% drug-loaded materials (333 °C). This is because of the higher drug loading percentage where interactions between

polymer and acetaminophen occurred to a greater extent when compared to lower drug loaded filament and tablet. Such intermolecular interactions affect thermodynamic properties of materials and material blends. A degradation was exhibited around 330 °C for all the PVA-containing samples and is assumed to be due to the reaction among oxygen-containing groups. The TGA data of drug-loaded filaments and tablets demonstrate that the ideal processing temperature of the materials used in this 3D printing project is up to 200 °C.

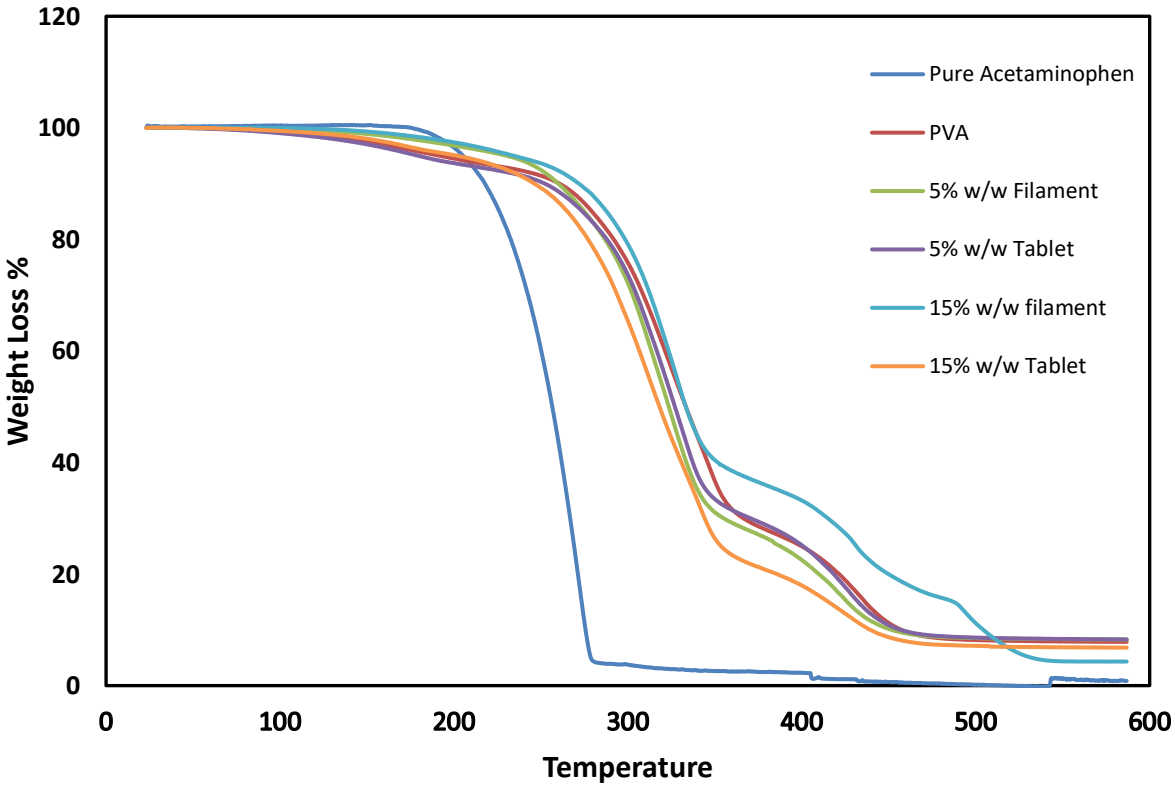

Figure 4-6: Overlay of TGA thermographs of (a) pure acetaminophen, (b) commercial PVA filament, (c) 5% drug-loaded filament, (d) 5% drug-loaded tablet, (e)15% drug-loaded filament, (f) 15% drug-loaded tablet.

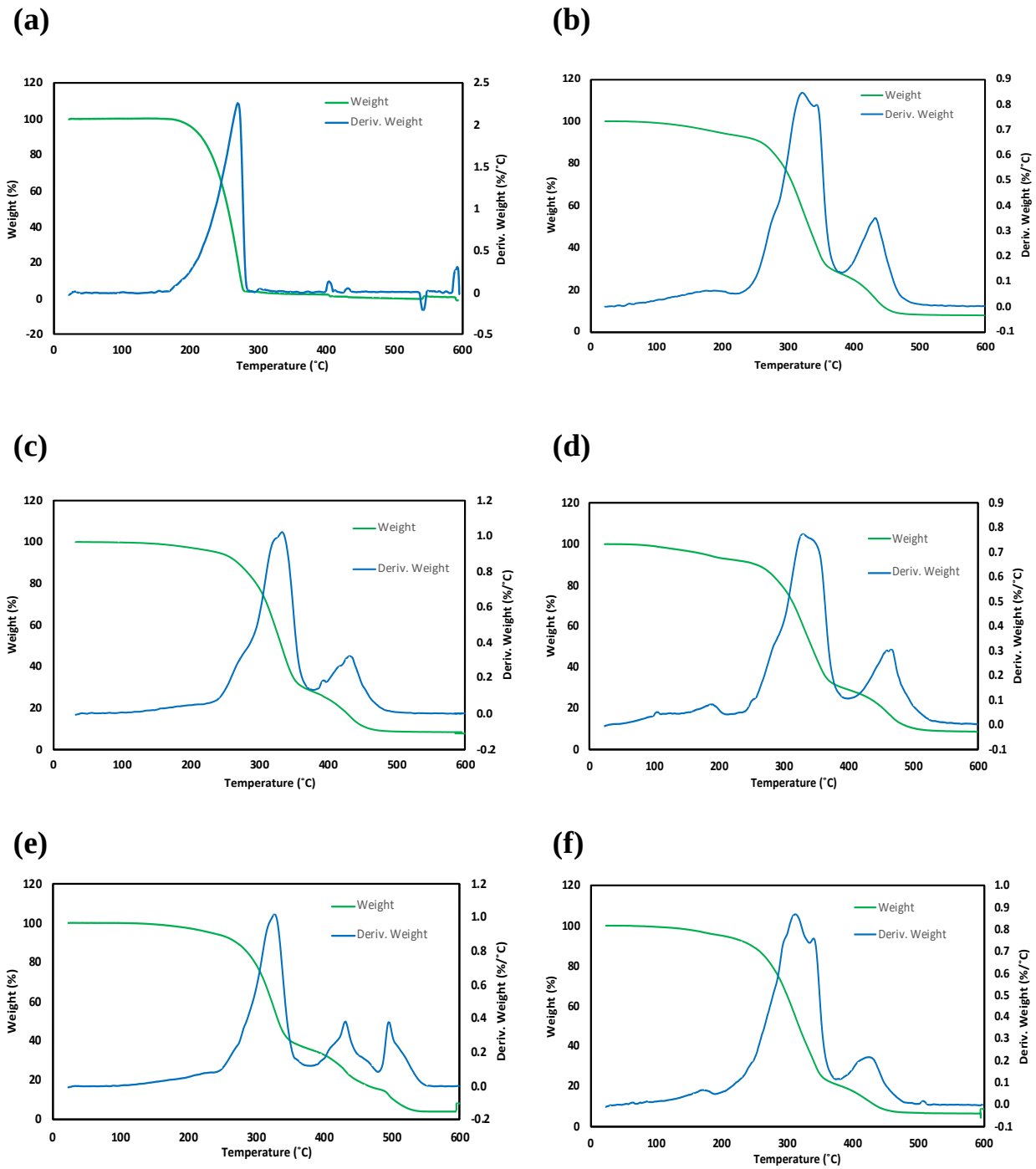

Figure 4-7: TGA thermographs of (a) pure acetaminophen, (b) commercial PVA filament, (c) 5% drug-loaded filament, (d) 5% drug-loaded tablet, (e) 15% drug-loaded filament, (f) 15% drug-loaded tablet.

4.6 ATR – FTIR Analysis

Infrared spectral data show that the characteristic peak positions remained stable in pure acetaminophen, PVA and the drug-loaded tablets, as shown in **Figure 4-8**. The major peaks of PVA spectra are at 3302 cm^{-1} (-O-H stretching vibration), 2920 cm^{-1} (-C-H stretching vibration), 1419 cm^{-1} (-C-H bending vibration), 1246 cm^{-1} (-O-H bending vibration), 1091 cm^{-1} (-C-O bending vibration). The broad and larger peak in PVA containing materials ranging from 3000 cm^{-1} to 3500 cm^{-1} is because of the abundant hydroxyl group present in PVA. However, the peak of pure acetaminophen at 3321 cm^{-1} (-N-H stretching vibration) was disappeared or blended in the broad peak of both the 5% and 15% drug loaded tablets, which might be because of the intermolecular reaction between -O-H and -C-H bonds (26). The peak at 2920 cm^{-1} and 2916 cm^{-1} for both the 5% and 15% drug loaded tablets respectively matched with the peak at 2920 cm^{-1} of PVA which confirms the presence of -C-H stretching vibration. The intensity of a peak seen at 2854 cm^{-1} in PVA decreased in the 5% drug loaded tablet and completely disappeared in 15% drug loaded tablet. This suggests that as PVA was emerging as the dominating material in the matrix, a molecular interaction, whose intensity increased and led to the disappearance of the peak at 2850 cm^{-1}.

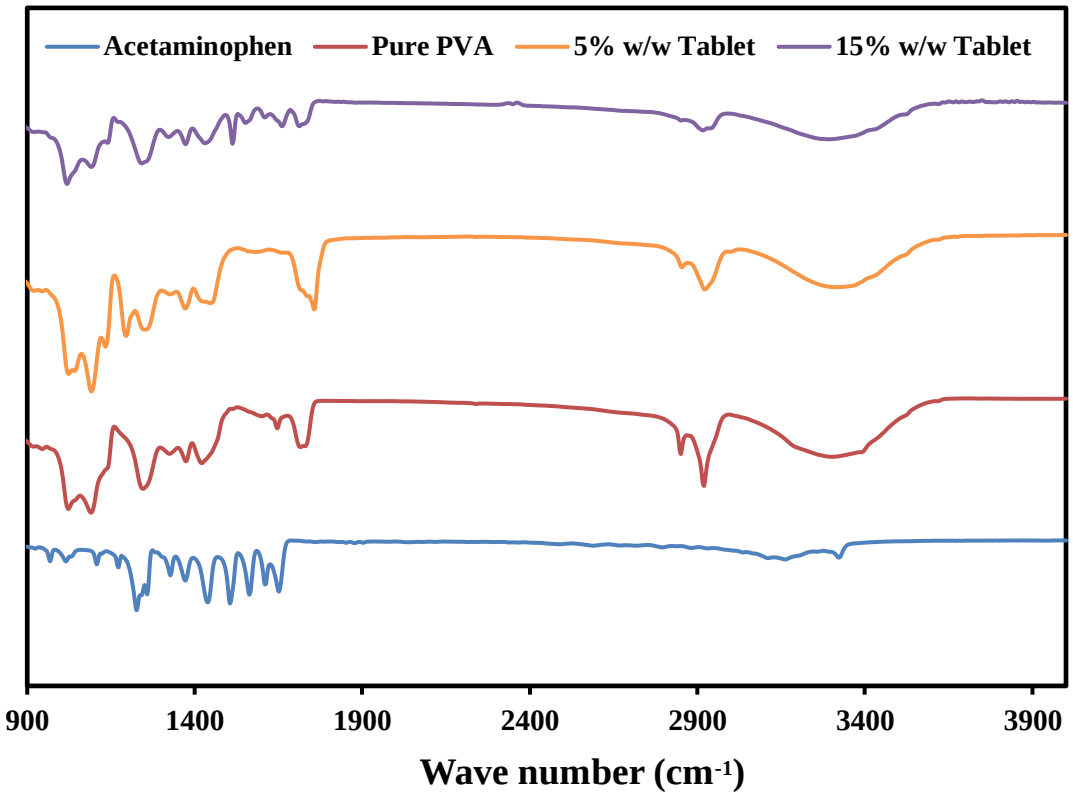

Figure 4-8: Overlay of FTIR spectra of pure acetaminophen, commercial PVA filament, 5% drug-loaded tablet, 15% drug-loaded tablet.

4.7 Weight Variation Test

According to USP <905> Uniformity of Dosage Units, a dose of the drug substance should be ≥ 25 mg which was justifiable with the printed dosage form, as shown in **Table 4.2**. The weight of the tablets did not vary with a constant infill percentage and the percentage deviation was also within the limit of 5%. The RSD of the weight of 15% drug loaded tablets were less than 5% confirming that these tablets with 15% drug loaded can be prepared with high reproducibility (58). The RSD of 5% drug loaded tablets and their

percentage deviation was slightly greater than the limit which is assumed to happen because of variation in filament diameter or because of loss of layers during 3D printing. Since the whole process is layer by layer FDM, it might be concluded that loss or addition of layers has caused the observed weight variation in 5% drug-loaded tablets.

Table 4.2: Weight variation test results of the 3D printed tablets

Tablet with Drug Loading Percentage	Average Weight (g)	Dose (g)	RSD %
5% (Cylinder)	0.512 ± 0.03	0.0256	6.33
15% (Cylinder)	0.499 ± 0.02	0.0748	4.61
15% (Capsule)	0.419 ± 0.01	0.0626	2.65

4.8 Thickness Test of Tablet

Tablet thickness of all 3 batches was matched with the Solidworks® design made for 3D printing. No noticeable change was observed in the case of 5% drug loaded tablets. The 15% drug-loaded capsule-shaped tablets were 0.4 mm thicker than the Solidworks® design (**Table 4.3**). During 3D printing, the machine had to stop and restart for some mechanical reasons, and this may have caused few more layers to be deposited by error to the tablets and the thickness became greater than the Solidworks® design. Percentage deviation came within ± 5% and RSD were also below 2% which indicates high reproducibility.

Table 4.3: Tablet thickness test results of the 3D printed tablets

Types of Tablets	Average Thickness (mm)	Thickness in Solidworks® Design (mm)	RSD (%)
5% Drug loaded	5.46 ± 0.05	5.00	0.93
15% Drug Loaded (Cylinder)	5.23 ± 0.02	5.00	0.48
15% Drug Loaded (Capsule)	3.90 ± 0.01	3.50	0.37

4.9 Friability Test of Tablet

The FDM 3D printed 15% drug-loaded tablets showed a percentage of weight loss of less than 1% and thereby meet the USP specifications, as shown in **Table 4.4**. A slightly more than 1% weight loss was observed in 5% drug-loaded tablet which was possibly because of loss of layers from the 3D printed tablets.

Table 4.4: Tablet friability test results of 3D printed tablets

Types of Tablets	Weight Loss (%)
5% Drug loaded	1.150
15% Drug Loaded (Cylinder)	0.540
15% Drug Loaded (Capsule)	0.405

4.10 Tablet Breaking Force Test

According to USP, tablets are accepted when they have resistance to breaking after sufficient strength and mechanical stress during transportation and storage. When tablets are compressed using a conventional system, the breaking force is then calculated according to the compression force. In comparison to that, the uses of binders control the breaking force of FDM 3D printed tablets (70). The breaking force of all three types of FDM 3D printed tablets exceeded the maximum detection range of 500 N. The tablets could sustain the larger force and was tough to break which is because of the layer-by-layer structure of the tablets and the denser grid design of the tablet (71). At some point, when 2nd force was tried after the 1st one, some layers of the 5% drug loaded tablet separated out and it was cracked into two pieces but still showed a value greater than 500N. No cracks or loss of layers were observed in 15% drug loaded tablets.

4.11 *In – vitro* Tablet Disintegration Test

The disintegration test was considered successful since all the tablets were disintegrated and passed through the mesh basket of the apparatus. FDM 3D printed tablets took a longer disintegration time than the usually compressed tablets which implies that zero-order release dosage forms can be designed using this concept (72). Since the tablets were printed at a high temperature, the bonds of the polymers are tightly agglomerated which took more time to break in DI water. A statistical analysis of disintegration times using ANOVA test, F (72.15) > F crit (5.14) demonstrated that the tablet disintegration

times were are significantly different (**Table 4.5)**. This suggests that the means of the disintegration times were not equal and at least one of them were different, which is seen in **Table 4.6**. Compared to 15% drug-loaded, the 5% drug-loaded tablets took more times to disintegrate completely; especially in the case of cylinder-shaped 15% drug-loaded tablet, they disintegrated in 10 min less time than cylinder shaped 5% drug-loaded tablet. This may be due to two possible reasons – 15% drug-loaded tablets have higher drug loading and less polymer percentage. 5% drug-loaded tablets have more polymer dominating than the acetaminophen present in it in comparison to the 15% drug loaded tablets. On the contrary, the 15% drug-loaded capsule-shaped tablets have fully disintegrated in 1 hour less time than the cylinder-shaped. The reason for this is assumed to be the average weight of capsule-shaped tablets is less than the cylinder-shaped tablet and also the thickness of the capsule-shaped tablets is less than the cylinder-shaped, which helped to have a faster disintegration time.

Table 4.5: One-way ANOVA test of tablet disintegration times of three different types of FDM 3D printed tablets

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	8016.66667	2	4008.33333	72.15	6.3618×10^{-05}	5.14325285
Within Groups	333.333333	6	55.5555556			
Total	8350	8				

Table 4.6: *In-vitro* tablet disintegration test results of the 3D printed tablets

Types of Tablets	Average Weight (mg)	Average Time to Disintegrate (hr:min)
5% Drug loaded	529	2 hr 55 min ± 8 min
15% Drug Loaded (Cylinder)	490	2 hr 45 min ± 7 min
15% Drug Loaded (Capsule)	420	1 hr 45 min ± 5 min

4.12 Drug Content

The data collected from HPLC were analyzed with EMPOWER software. The theoretical concentration is calculated using the **Equation 4.1** below -

$$C_1V_1=C_2V_2 \quad (4.1)$$

The drug content of filaments was found to be low when compared to drug loaded tablets **Table 4.7**. It might be due to uneven distribution of drug throughout the filament. The percentage loss in drug loaded samples is because acetaminophen starts to degrade above 200 °C as was seen in TGA analysis. Recall that, these tablets are printed at 240 °C and the drug-polymer blend was first extruded into a filament which was then 3D printed. The high temperature used during tablet processing can lead to the observed drug loss. Manually, mortar and pestle were used for mixing the acetaminophen with crushed PVA powder; this might be another occasion where drug loss has occurred. The cumulative drug degradation and loss occurring during extrusion and printing and the blending process are possible reasons for the loss of drug during tablet printing.

Table 4.7: HPLC analysis of drug loaded filaments and the 3D printed tablets

Sample	Theoretical Drug Content	Drug Content with HPLC
5% Drug loaded Filament	5%	0.07%
5% Drug loaded Tablet	5%	0.5%
15% Drug loaded Filament	15%	2%
15% Drug loaded Tablet	15%	2.3%

Chapter 5

Summary

5.1 Conclusion

A systematic study was conducted on formulating acetaminophen using polymer based FDM 3D printing. Choice of the model drug – acetaminophen USP, was based on its viable characteristics to assay the effect of PVA as a drug carrier while subjected to different temperatures. The operation required hot-melt extrusion (HME) of drug-loaded filaments which were fed into the 3D printer to fabricate tablets. A relatively high temperature, around 195 °C was used to extrude the filaments while a temperature around 240 °C was necessary to print the tablets loaded with 5% w/w acetaminophen and 15% w/w acetaminophen separately. In the future, the extrusion and printing temperature could be reduced using a plasticizer such as polyethylene glycol. Two geometrical shapes of tablets; cylinder shaped 5% and 15% drug-loaded tablets and capsule shaped 15% drug-loaded tablets were successfully printed. The geometrical shape and drug loading percentage was found to produce notable variances in DSC, TGA, SEM, FTIR and physical, and mechanical characterization. The characteristic peak of acetaminophen disappeared or blended in both drug-loaded tablets due to the intermolecular reaction

between N-H, -O-H and -C-H bonds of acetaminophen and PVA as confirmed by FTIR analysis. The drug loading percentage was minimal and PVA was the dominating material in 5% drug-loaded tablet. Through SEM analysis, compared to the cross-section of commercial PVA filament, a rough and abrupted surfaces was observed in the cross-sections of drug-loaded filaments and tablets. DSC and TGA analysis confirmed the thermal stability of 3D printed tablets at the extrusion temperatures although a notable amount of drug content loss was quantified with HPLC analysis. Decreasing the processing temperature and increasing the drug percentage could be helpful to overcome this loss. Although the tablets passed all the mechanical and physical characterization according to USP guidelines, a distinct difference in *in-vitro* disintegration time was seen. Capsule-shaped tablets disintegrated faster than cylinder shape; also, a longer disintegration time was noted with FDM 3D printed tablets than conventional compressed tablets. This implies that geometrical shape is a factor that can impact the pharmacokinetic profile of tablet dosage form and 3D printed tablets may be a suitable design for a zero-order release formulation. Beyond all the challenges to fabricate FDM 3D printed tablets, the main focus of this project was investigating the feasibility of this process, which was successful. It is hoped that this study will set the groundwork for further research on exploring the potential of 3D printed tablets as a drug delivery system.

5.2 Future Prospect of the Study

Personalized medication system using FDM 3D printing technology could create promising opportunities in the pharmaceutical industry, including enhanced patient compliance. PVA is acting as a suitable polymer for fabricating 3D printed tablets while

tailoring the drug release profile from the tablets (26). This can be used to design new dosage form of medication with specific pharmacokinetic profile. Preliminary results obtained from the disintegration studies indicate this technology can be adapted to design delayed release formulations. Formulating multiple prescribed drugs in one single dosage form could be challenging in convention tablet manufacturing, while FDM 3D printing technology can be helpful to manufacture such solid oral dosage forms. Thus, dosing regimen according to the pharmacogenetic profiles of a particular patient group can be attained (73). From industrial point of view, 3D printing of tablets has less processing steps than conventional tablet making processes (74). From the analysis of *in-vitro* tablet disintegration, it can be said that sustained and/or delayed release dosage forms can be engineered with FDM 3D printing technology in the future studies. Using a plasticizer such as various molecular weight PEG could reduce the extrusion temperature of drug loaded filaments and tablets, which implies that thermo-sensitive APIs could be delivered using this FDM process. Additional studies are necessary to further understand the presence of imperfections and the porosity of the formulation matrix.

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