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# Lidocaine Mucoadhesive Film Fabrication Using Fused Deposition Modeling 3D Printing

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# LIDOCAINE MUCOADHESIVE FILM FABRICATION USING FUSED DEPOSITION MODELING 3D PRINTING

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## ABSTRACT

Hot-melt extrusion and 3D printing are among the recent means of processing techniques adopted in the pharmaceutical industry. These technologies are used to as a method of preparing solid dispersions develop complex shapes that are difficult to be obtained using other means of production. In the current research work, many formulations loaded with lidocaine HCl were prepared and extruded using 11mm twin-screw extruder. The extrudate filaments were then fed into a fused deposition modeling (FDM) printer to fabricate mucoadhesive films meant to buccal applications to manage local pain within the oral cavity that requires the intervention with local anesthetics. The printed films drug content was determined using HPLC, films drug content was within the acceptable limits. Furthermore, the drug release was assessed using an in-house method. All test formulations revealed an excellent release profile of the lidocaine HCl, reaching more than 90% within 5-15 min. The films adhesion and mechanical properties were tested using texture analyzer. The results indicated that the films possess an adequate mechanical property to satisfy its intended use. In conclusion, this research work demonstrates that coupling hot-melting extruder to a fused deposition modelling printing is feasible to produce lidocaine-loaded buccal mucoadhesive films intended for local application in the oral cavity.

## DEDICATION

I dedicate this work to my family and friends. I'm especially grateful for my parents Yahya and Awatif whose words and backing encouraged me to stay ambitious. My brothers Abdullah and Abdulaziz and my little sister Nora for their unmatched support throughout this phase. I'm equally grateful for my beloved wife Abeer for everything she did. And I also dedicate my work to my late friend and colleague Muteb Alharbi

## ACKNOWLEDGMENTS

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## CONTENTS

## LIST OF FIGURES

## LIST OF TABLES

# CHAPTER 1

# INTRODUCTION

Hot-melt extrusion (HME) has been known since 1930s and is widely used in the plastics industry (Chokshi & Zia, 2014). HME was recently adopted in the pharmaceutical industry mainly as a method of creating pharmaceutical solid dispersions. HME, as the name indicates, is based on the combining of heat treatment, mixing of materials and extruding the molten material throughout an orifice (i.e., pressurizing the materials) where combining these factors in a controlled manner exerts the required stress on the treated material to change some of its physical and physicochemical criteria, which will serve the purpose of enhancing the performance of the material in question. (Bruin, Van Zuilichem, & Stolp, 1978)

From an engineering point of view, there are two types of extruders, a) single screw extruder and b) twin screws extruder, based on the number of screws used in the process (Maniruzzaman, Boateng, Snowden, & Douroumis, 2012). Both types consist of the same functional parts, which are feeding zone, barrel (in which the elements-loaded-shafts reside and rotate to convey and mix the materials), and discharge zone (in this zone different dies can be accommodated to yield different shapes of extrudate). When it comes to the elements-loaded-shafts, it could be assembled into numerous configurations each to serve the desired purpose sought by the user. Figure 1 shows two examples of how a screw could be assembled.

This diversity in the machinery, in terms of classes, screws configurations, feeding zone location, temperature, and speed, gives HME more advantages and preference, since it can be employed for different applications (Repka, Majumdar, Battu, Srirangam, & Upadhye, 2008). There are other advantages for HME in the pharmaceutical applications, such as its suitability for continuous processing, it is a solvent-free process of making solid dispersions, and the equipment costs are lower with a smaller footprint compared to other processing equipment used in the pharmaceutical industry (Kolter, Karl, & Gryczke, 2012)

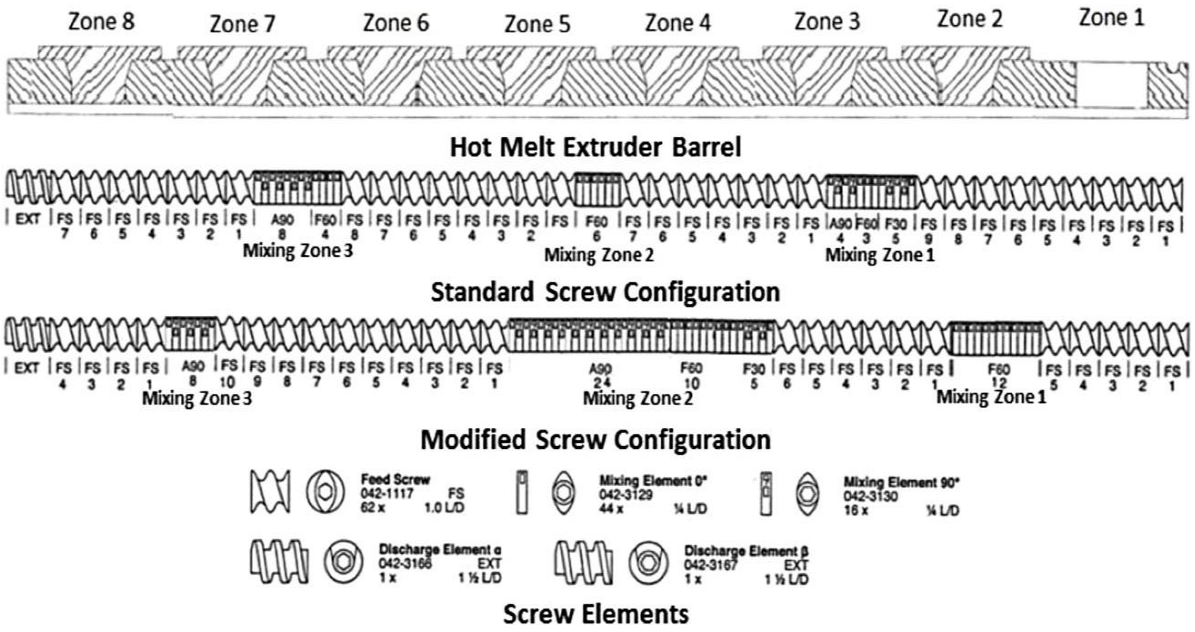


Figure 1 HME Screw Configurations

## 3-Dimensional Printing

3-Dimensional Printing (3D printing or 3DP), also known as additive manufacturing, is a technique used to fabricate objects from an electronic data model – usually created using Computer-Aided Design (CAD) software-. The fabricated objects are often challenging to create by conventional methods (e.g., objects with complex geometrical properties). 3DP creates such objects by laying one layer over another layer in accordance with the CAD model (Ngo, Kashani, Imbalzano, Nguyen, & Hui, 2018). One of the earliest types of 3D printers (Stereolithography printer) was introduced for commercial use in the late 1980s by 3D Systems (Wohlers & Gornet, 2016), 3D Systems is considered a pioneer in the development, engineering, and manufacturing of 3D printing techniques through its internal research and partnerships with other companies specialized in creating other techniques of 3D printing (3D-Systems, 2020). This fabrication technology has been used in a wide array of fields from construction, to rapid prototyping, to the bioprinting of biological tissues (Lee & Yeong, 2016; Tay, et al., 2017).

Additive manufacturing is classified into seven major classes based on the mechanism of layering and curing of materials. The first class is directed energy deposition, which includes laser engineered net shape, direct metal deposition, direct light fabrication, and 3D laser cladding. This class employs the most complex fabrication methods, since it relies on a direct energy source to bind the layers together. The second class is sheet lamination, which includes laminated object manufacturing (LOM) and ultrasonic additive manufacturing (UAM). The third class is powder bed fusion, which has five techniques to print; this class use electron beam or laser to fuse the powder particles. Selective laser melting (SLM), direct metal laser sintering (DMLS), selective

heat sintering (SHS), electron beam melting (EBM), and selective laser sintering (SLS) are techniques of powder bed fusion class. The fourth class is material jetting, where the material is jetted through a printing head onto a platform to the specified CAD model and allowed to cure by exposing it to UV light. Plastics and polymers such as high-density polyethylene (HDPE) and polypropylene are used as printing material in material jetting 3DP. The fifth class is binder jetting, which involves two materials, binder material and powder material, where the binder material functions as an adhesive agent sandwiched between powder layers. The sixth class is photopolymerisation, where focused UV light is used to cure photosensitive polymer resin. The seventh class, and the one used in this project, is material extrusion, where a thermoplastic filament is fed into a printing head in which the temperature is elevated in a controlled manner to soften the filament then shape it into the desired geometry. This technology is also known as fused deposition modeling (FDM) (ASTM, 2012; Kruth, 1991; Wong & Hernandoz, 2012).

**Buccal Dosage Forms**

One can administer medicament into patients by numerous means. However, the easiest and the preferable mean of administration is the oral route. Because solid and liquid active pharmaceutical ingredients (API) could be administered orally to exert local effect in the oral cavity and along the gastrointestinal tract (GIT) or systemic effect as long as the API will be sufficiently bioavailable in systemic circulation at a therapeutic level. One of the barriers to achieving sufficient bioavailability following oral administration of some APIs is significant hepatic clearance (known as first-pass effect). This issue has motivated pharmaceutical scientists in academia and industry to continuously seek practical solutions to overcome the effect of the first-pass metabolism of certain orally administered APIs (Drummond, Rathbone, & Tucker, 1994).

Among the solutions to the problem of the first-pass effect, is shifting the absorption site for the API from the GIT to the oral cavity because of the high vascularity of the oral cavity that directly access to the systemic circulation, which allows direct absorption into the systemic circulation without crossing the hepatic environment. In this vein, in the past 30 years researchers have been intensively studying the suitability and the extent of the lining of the oral cavity, called the oral mucosa, to absorb APIs. The anatomy of the oral mucosa that lines the oral cavity consists of two main layers, epithelium layer backed by arteries and veins rich connective tissue layer. The epithelium is made out of five layers that are mucus layer, stratum distendum, stratum filamentosum, stratum suprabasal, and stratum basal; whereas the connective tissue consists of lamona propria and is backed with a submucosa as illustrated in Figure 2 (Rathbone, Senel, & Pather, 2015).

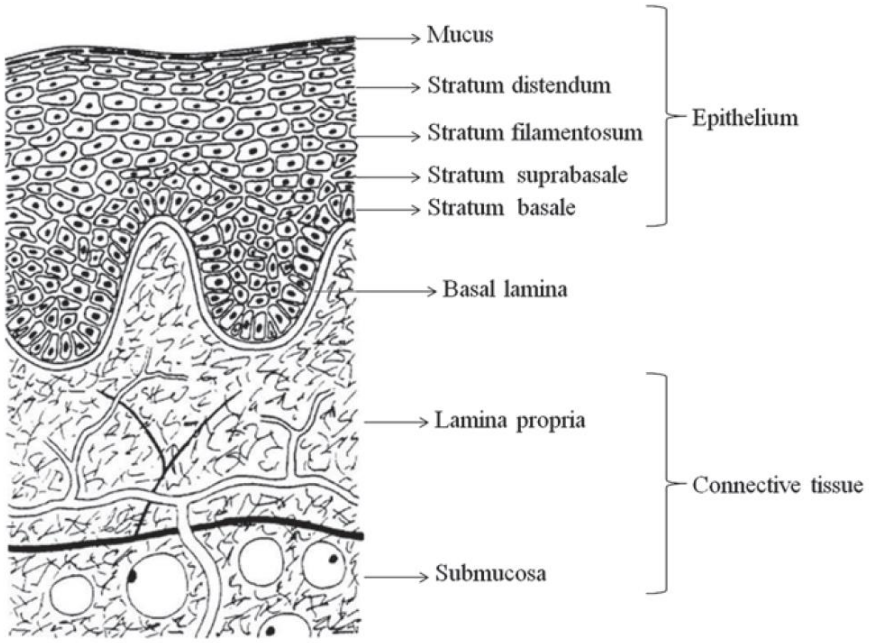


Figure 2 Cross-Section of the oral Lining Histology

The total surface area of the oral cavity is reported to be approximately 170 squared cm (Colllins & Dawes, 1987), which is relatively small compared to other effective absorption sites such as the stomach and the intestines. This makes the systemic bioavailability of the API that intended to be absorbed in the oral cavity relatively low. Even though the absorption area in the oral cavity is relatively smaller, it still yields better bioavailability compared to topical route (Du, Liu, Salentinin, Nguyen, & Boyd, 2014; Squier & Rooney, 1976)

John Smart (1993) believes that the oral mucosa, despite its high vascularity, is a significant barrier that hinders the systemic absorption of the large theraputic molecules but a suitable rout for local delivery within the oral cavity. It has been shown that patients who sufer chronic injuries within the oral cavity and prescribed a mucoadhesive-dosage-form, do not adhere to the regimen for the long term use. The incompliance is attributed to the lack of physical flexibility of the commercially available dosage forms (Hearnden, et al., 2012). thus finding a more acceptable alternative to improve patients compliance is required.

Considering the anatomical and physiological nature of the oral cavity and its lining, pharmaceutical scientists considered some design criteria of dosage forms intended for oral administration and to be absorbed in the oral cavity such as sublingual tablets, buccal mucoadhesive films and buccal mucoadhesive tablets. Where it should be manufactured in a manner that enhances patient compliance as well as improves the acceptability of such delivery systems as an alternative for the conventional oral solid dosage forms. One agreed upon criterion is that a mucoadhesive dosage should be unobtrusive and easy to place in the oral cavity and must be fabricated in a patient-friendly way that does not eating, tasting and speech . Another agreed upon concept is that the excipients embedded in the formulations should not irritate the mucosa to

prevent excess saliva section which will results in API wash-out and prevent its availability for absorption (Anders & Merkle, 1989).

This research project is an attempt to couple the HME and FDM 3D printer to produce lidocaine HCl mucoadhesive films for local oral application targeting oral ulcers and other wounds. This coupling could open the opportunity for continuous manufacturing process of the mucoadhesive film based on some of the quality by design (QbD) requirements to ensure the quality of the outputs.

Lidocaine HCl is a white odourless powder. Lidocaine HCl has a melting range between 74-79°C (USP 29) and water solubility of 0.69 g/ml at room temperature. Lidocaine HCl is physicaly and chemically stable in the solid form. However, in solution it has been proven that it degrades mainly by hydrolysis (Groningsson, Lindgren, Lundberg, Sandberg, & Wahlen, 1985).

# CHAPTER 2

# METHODOLOGY

## Materials

Lidocaine HCl (API) and polyethylene glycol 3350 were purchased from Spectrum Chemical Manufacturing Corporation (New Brunswick, NJ, USA). PolyOx™ N80 LEO NF (PEO N80), hypromellose HME grade (HPMC), and hypromellose acetate succinate 716 (HPMC-AS) were obtained as gifts from ColorCon Inc. (West Point, PA, USA). All other chemicals and solvents were of an analytical grade and purchased from Fisher Scientific (Hanover Park IL, USA).

## Formulations Composition

Different formulations were prepared based on the screening design. Each excipient in the formulation was set into two levels (Table1). The concentrations of Lidocaine HCl was fixed at 10% (w/w) for each formulation. Based on the number of components and levels of each component, 16 formulations were suggested (Table 2).

Table 1 Excipients Levels

| | high [+] | low [-] |
|---|---|---|
| PEO | 8 | 5 |
| HPMC | 3 | 0 |
| HPMC-AS | 4 | 0 |
| PEG | 2 | 0 |

Table 2 Formulations composition as per the Screening DoE (%w/w)

| Formulation code | PEO N80 | HPMC | HPMC-AS | PEG | Total parts | Lidocaine HCl |
|---|---|---|---|---|---|---|
| F1 | 8 | 3 | 4 | 2 | 17 | 10 |
| F2 | 8 | 3 | 4 | 0 | 15 | 10 |
| F3 | 8 | 3 | 0 | 2 | 13 | 10 |
| F4 | 8 | 3 | 0 | 0 | 11 | 10 |
| F5 | 8 | 0 | 4 | 2 | 14 | 10 |
| F6 | 8 | 0 | 4 | 0 | 12 | 10 |
| F7 | 8 | 0 | 0 | 2 | 10 | 10 |
| F8 | 8 | 0 | 0 | 0 | 8 | 10 |
| F9 | 5 | 3 | 4 | 2 | 14 | 10 |
| F10 | 5 | 3 | 4 | 0 | 12 | 10 |
| F11 | 5 | 3 | 0 | 2 | 10 | 10 |
| F12 | 5 | 3 | 0 | 0 | 8 | 10 |
| F13 | 5 | 0 | 4 | 2 | 11 | 10 |
| F14 | 5 | 0 | 4 | 0 | 9 | 10 |
| F15 | 5 | 0 | 0 | 2 | 7 | 10 |
| F16 | 5 | 0 | 0 | 0 | 5 | 10 |

To minimize the number of formulations handled, eight formulations were selected for processing and testing. The final candidate formulations are F2, F3, F5, F8, F9, F12, F14, and F15.

**Film Preparation**

**Hot-Melt Extrusion**

The HME process was conducted using Thermo Scientific™ Process 11 Parallel Twin-Screw Extruder by Thermo Fisher Scientific (Waltham, MA, USA). The produced extrudate processed at 140℃ (including Die), Screws speed of 50 RPM and the feeding rate between 1 – 2 gm/min. The extruder was equipped with 1.7 mm die to produce filaments with suitable diameter for 3D printing.

**3D Printing**

The 3D printing step was carried on Prusa i3 MK3 printer (Prague, Czech Republic). The printing head temperature was set at 200℃ while the printing bed temperature was set on 40℃. The desired shape of the printed film is a cylinder with 6 mm radius and 0.24 mm thickness. The dimensions were entered into an on-line designing webpage (TINKERCAD©), the design was sliced via Cura© software from Ultimaker (Utrecht, Netherlands).

Every formulation was printed in three different infill percent (40%, 70%, and 100%) and every infill was printed in two infill patterns (grid shape & lines shape), thus every successful formulation is printed in 6 different configurations as shown in Table 3.

Table 3 3DP Film infills and patterns

| Infill / Pattern | 40% | 70% | 100% |
|---|---|---|---|
| Lines | ✓ | ✓ | ✓ |
| Grid | ✓ | ✓ | ✓ |

Once the filament is fed and fixed correctly into the printing-head, the printing-head was allowed to reach the required printing temperature of 200°C, then printing to the specified shape starts.

**Three-Point Bend Test**

Using Texture analyzer (TA) TA.XT2i (Stable Micro Systems/Texture Technologies Corporation, London, UK) equipped with TA-92N Three-Pint Bend Rig, a 6 cm specimens (n=4) of extruded filaments were placed on the rig, a testing knife is lowered to be in contact with the

specimen and force was exerted until the specimen broke. Samples were deemed acceptable if it broke after 1 sec of applying the force (Zhang, Feng, Patil, Tiwari, & Repka, 2017).

**Drug Content**

Samples of physical mixtures, extruded filaments and 3D printed films were analyzed (n=3) to assure the drug content and uniformity. The weighted samples (approximately 15-25 mg each) were dissolved in 20 mL methanol then diluted 10 times and analyzed using High Performance Liquid Chromatography (HPLC).

**Differential Scanning Calorimetry (DSC)**

The physical state of the API, excipients, HME extruded filament, and the 3D printed films were assessed using TA Instruments (New Castle, DE, USA) where 3 -5 mg samples were placed in Tzero pan sealed with accompanying lid. The loaded pan then placed in the DSC. The DSC was set to equilibrate at 30°C then to stay in Isothermal state for 1 minute, afterward start to ramp 10°C / min until it reaches maximum of 200°C.

***In Vitro* Release**

The Lidocaine HCl release profile of different 3D printed films was studies using an in-house method. Since there is no compendial method and apparatus to study the release from mucoadhesive films, the literature is rich with customized in-house methods and apparatae to study the release profile of various APIs (Eleftheriadis, et al., 2019). The in-house apparatus is a 60 mL tube filled with 50 mL Saliva Simulating Fluid (SSF) as a release media, the SSF consists of sodium chloride, potassium phosphate monobasic, and sodium phosphate dibasic, kept under continuous stirring at 37℃ and pH of 7.2.

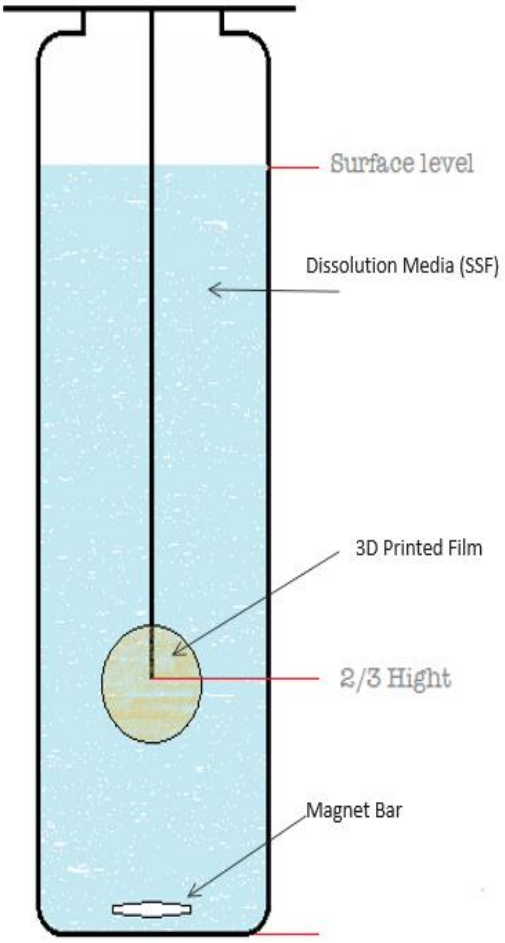


Figure 3 In-house Release Apparatus

Films (n =3) immersed and held at a reasonable depth in the SSF release media by a supporting shaft as it shown in Figure 3. A sample of 1 mL is withdrawing then replaced with fresh quantity of SSF at predetermined time points (0, 5, 10, 15, 30, 45, 60, 90, and 120 min). HPLC was used to analyze the samples.

**HPLC analysis**

The HPLC analysis was performed using Waters HPLC-UV system (Waters Corporation, Milford, MA, USA). Luna C8 (5µ) 150x4.6 mm column was used. The composition of the used mobile phase was Methanol: 25mM Dibasic Potassium Phosphate (k2HPO4) buffer in 70:30 % (v/v). The pH was adjusted to 6.8 using o-phosphoric acid. The lidocaine HCl was detected by using 20 µL injection volume and 0.8 mL/min flow rate at 225 nm. Under these analytical conditions, the lidocaine HCl retention time of approximately 6.3 minutes. The method linearity was validated over wide range of lidocaine HCl concentrations (1, 5, 10, 25, 50, and 100 µg/mL) and the $R^2$ was 0.9999.

**Film Strength**

Using Texture analyzer (TA) TA.XT2i (Stable Micro Systems/Texture Technologies Corporation, London, UK) equipped with TA-108S-5 Probe, a 150x15mm 3D printed film was placed on the holding tray with holes beneath the film to allow the probe to pass through the film and measure the required force to break through the film. Once fixed on the tray the test is run in the following TA conditions:

- Pre-test speed = 2.00mm/sec.
- Test Speed = 1.00 mm/sec.
- Distance = 10.0 mm.
- Trigger force = 10.0 g.
- Break sensitivity = 50 g.

**Folding Endurance**

Folding endurance is a test to assess the mechanical elasticity of the film, where a film strip is fixed on surface and then folded 90° repeatedly in the same point until the film at this point comes to full break (Irfan, et al., 2016). 3D printed films (n=3) of each formulation were fixed then manually folded 90° repeatedly until complete break of the film. The number of foldings until the sample broke was reported.

**Adhesion**

Using Texture analyzer (TA) TA.XT2i (Stable Micro Systems/Texture Technologies Corporation, London, UK) equipped with TA-57R 7mm Die, 1" radius prop, the adhesion study was conducted as follows: a 150x15mm 3D printed film was wetted for 30 seconds and 5 min by SSF then the wetted film is placed on a holding tray. Once fixed on the tray the test starts as per the following conditions:

- Pre-test speed = 1.00mm/sec
- Test Speed = 1.00 mm/sec
- Applied Force = 356.9 g
- Return Distance = 10 mm
- Contact time = 5 sec
- Trigger Type = Auto
- Trigger Force = 51.0 g
- Tare mode = Auto

Figure 4 is a schematic presentation of the workflow in this research project. Figure 4 and summarizes the processes and the related tests in respect to each other.

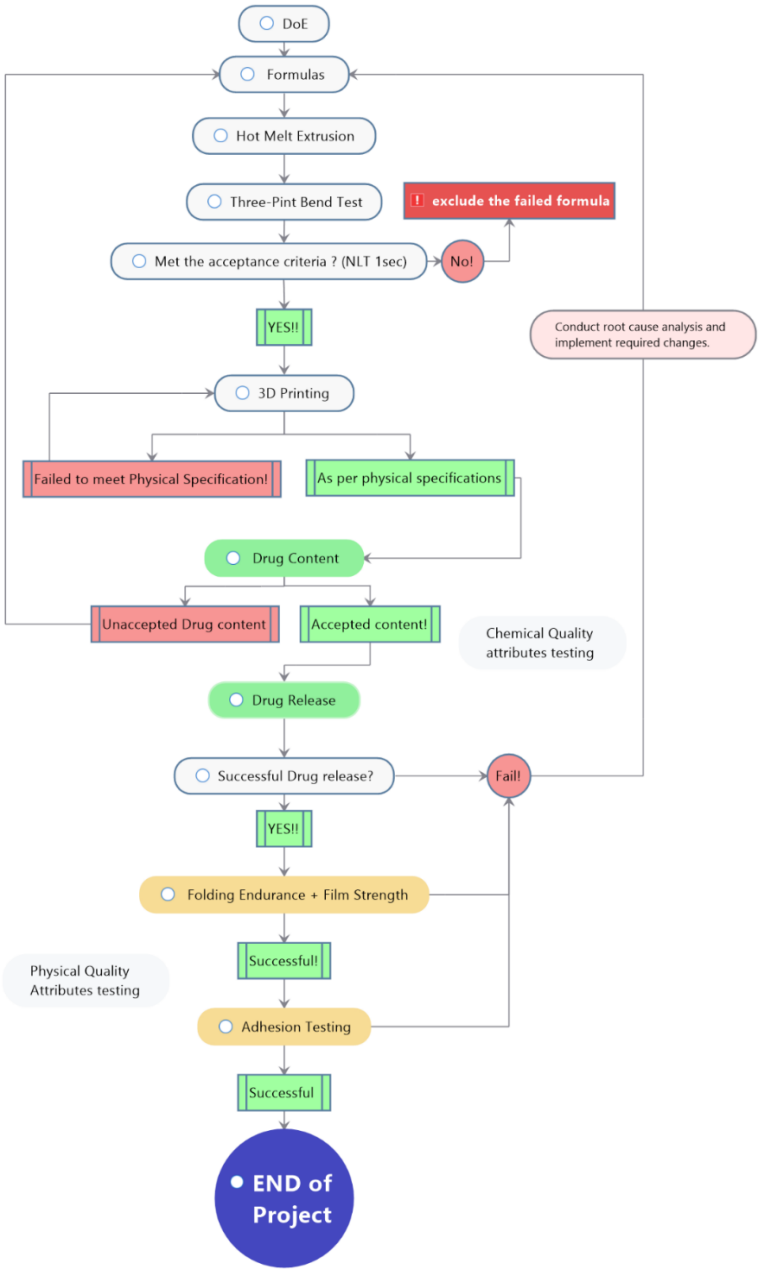


Figure 4 Project Flow Chart

# CHAPTER 3

# RESULTS AND DISCUSSION

## Film Preparation

### HME

The screw configuration identified as “standard” on Figure 1 was used. The torque in all processed formulations was between 25 -37 per cent which indicates that the formulations were malleable enough and suitable for HME processing. The obtained filaments were faint yellow to light brownish yellow depending on the formulation composition, all filaments showed similar texture and were smooth to the touch.

## Three-Point Bend Test

This test was conducted to assess the extruded filament suitability for 3D printing process, formulations that failed this test were disqualified for further processing. Of every formulation 4 samples (n=4) underwent the test and the time to break should not be less than (NLT) 1 sec because any filament that breaks in less than 1 second is deemed fragile and could break inside the 3D printer and clog it. Table 4 shows the results of three-point bend test of the extruded formulations.

Table 4 Three-Point Bend results

| Formulations | Time (sec) n=4 | S. D |
|---|---|---|
| F2 | 1.76 | 0.21 |
| F3 | 1.75 | 0.18 |
| F5 | 1.73 | 0.06 |
| F8 | 1.74 | 0.29 |
| F9 | 1.76 | 0.05 |
| F12 | 0.44 | 0.06 |
| F14 | 1.74 | 0.07 |
| F15 | 1.61 | 0.01 |

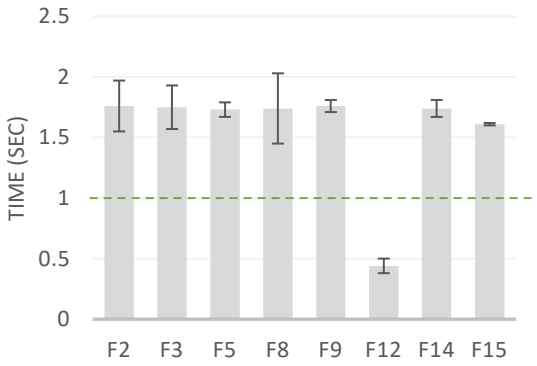


Figure 5 Three-Point Bend results

All formulations, except F12, exceeded the 1.5 sec mark, which allows them to have the necessary stiffness to be fed and processed in the 3D printer. Thus, F12 was excluded because it failed to meet the acceptance criteria (i.e. out of Specifications) of NLT 1 sec and broke at 0.4 sec.

**3D Printing**

The physical appearance of the 3D printed films was a porous cylindrical film with a 6 mm radius and 0.24 mm thickness. Using the online designing software (TINKERCAD©) and

the slicing software Cura© software from Ultimaker (Utrecht, Netherlands), the following was entered for the printing dimensions:

- X axis = 12 mm.
- Y axis = 12 mm.
- Z axis = 0.24 mm.
- Layer Thickness = 0.06 mm.
- Wall Thickness = 0.8 mm.
- Wall number = 1

Formulations F2, F3, F5, F8, F9, F14, and F15 extrudates were examined for diameter uniformity because during the extrusion process some variability in the diameter occurs due to pull tension during the filament collection step. Once the diameter uniformity of the filament is proven satisfactory, the 3D printing step starts by feeding the filament into the FDM 3D printer.

Films printed from formulations F3, F5, F8, F9, and F15 couldn't maintain the physical shape specifications because of the viscosity being too high to be printed and shaped. whereas formulations prepared with the lower level of plasticizer were too fragile so that they broke during the feeding in the 3D printer, thus they were not suitable for the project's objective. Only formulations F2 and formulation F14 succeeded to meet the specified physical shape and to maintain the suitable physical strength to be handled for further testing. The final 3D printed film of F2 and F14 is depicted in Figures 6 and 7, respectively.

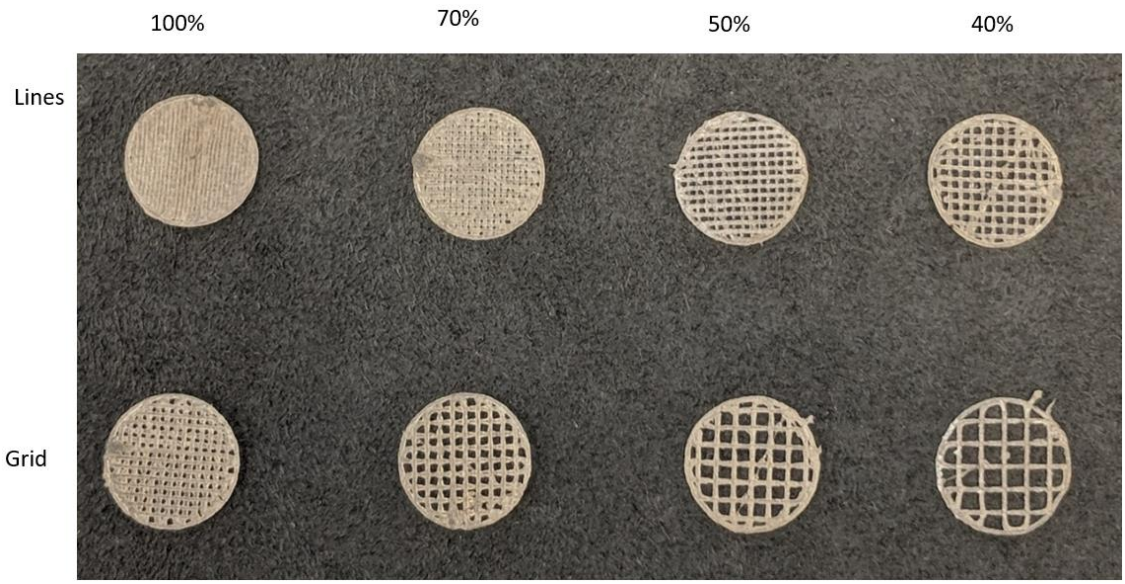


Figure 6 F2 3DP films

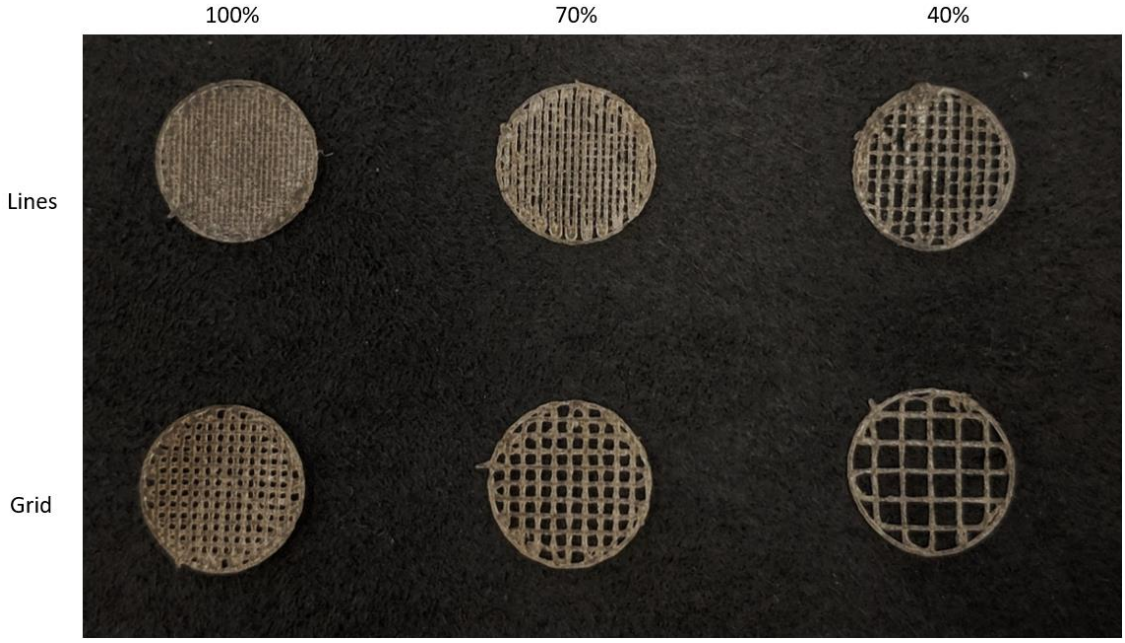


Figure 7 F14 3DP films

**Drug Content**

The drug content of filaments before 3D printing was within the acceptance limits. As Table 5 and Figure 8 shows, the API content in formulation F2 was 90%±6.92, which is at the lower borderline of the acceptance limit. The F14 content was around 94%±7.63. Possible reasons for the low assay values are discussed below

Table 5 Filaments Content of Lidocaine HCl

| Filament | Content % (n=3) | S. D |
|---|---|---|
| F2 | 90.00 | 6.92 |
| F14 | 94.00 | 7.63 |

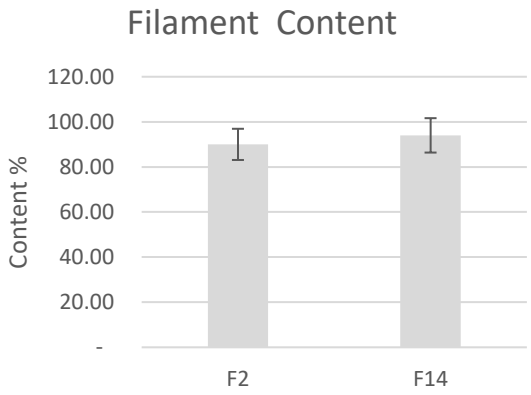


Figure 8 Filaments Content of Lidocaine HCl

The 3D printed films' content was uniform throughout the different infill percent of F2 films around 88% of the label claim, which is 2% lower than the filament content before printing this reduction in Lidocaine HCl content pre- and post 3D printing process was expected because of the repeated exposure to different processing force. In the other hand, the drug content of F14

3D printed films of 40% and 70% infills were about 6% less than the filament where the 3D printed films content was 88% and 90%, respectively. However, the 100% infill films of formulation F14 showed extremely lower content (more than 10% lower) compared to the other 3D printed films of 40% and 70% infill, wherein it was expected that the 100% infill to show the highest content of them all since it's the one with more material and weight in it. The 100% infill content was 79% (i.e. 14% lower than the filament content before printing) which could be attributed to various reasons, such as 3D printing using filament part with initial low load of the API due to non-uniform mixing and distribution , but this reason was ruled out since the other two infills were 3D printed using the same filament and with a reasonable content, therefore if it was true one of the other infills should've shown relatively higher content to balance the non-uniform API distribution out.

Other possible cause of low content in the 100% infill films is that the incomplete extraction of the API from the tested films which resulted in the observed lower content. Regardless of the content of the 100% infill printed film of F14, the content of the remaining 3D printed films of both formulations deemed satisfactory as shown and depicted in Table 6 and Figure 9 below.

Table 6 3DP Films Content of Lidocaine HCl

| | Infill (%) | Content (%) (n=3) | S. D |
|---|---|---|---|
| F2 | 40 | 88.53 | 1.52 |
| | 70 | 88.63 | 0.04 |
| | 100 | 88.28 | 4.18 |
| F14 | 40 | 88.04 | 4 |
| | 70 | 90.06 | 6.89 |
| | 100 | 79.23 | 2 |

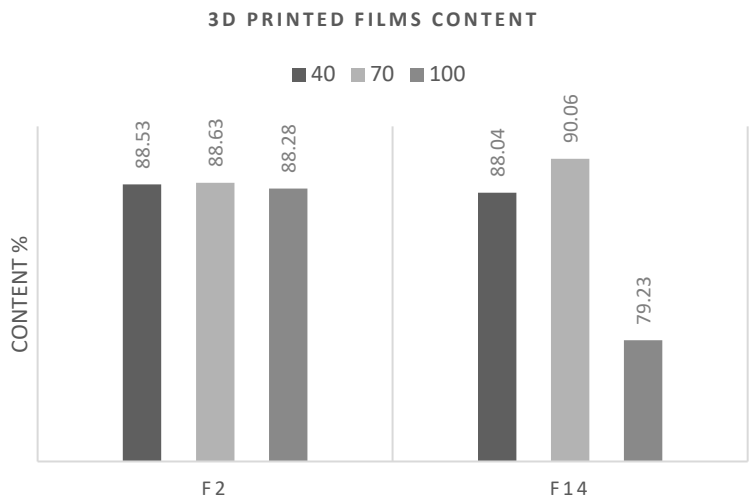


Figure 9 3DP Films Content of Lidocaine HCl

**DSC**

The final pharmaceutical product in this project is exposed to relatively elevated temperatures during different manufacturing steps. therefore, phase transition is of great importance to be checked in the different stages of the manufacturing of the 3D printed films. DSC was conducted for Pure API as well as pure excipient before conducting it for every formulation in its different forms as Physical mixture, Filament, and 3D printed films.

API, Lidocaine HCl, melting point is around 80°C (NIH, 2020), the DSC analysis show a peak for the pure API corresponding to that melting point, Relatively smaller peaks are seen in the physical mixtures of both formulations and that could be attributed to the small load of the API in the final formulation (10%). However, the API peak disappears after exposing to elevated temperatures as seen in extruded filaments and 3D printed Films, which indicates Lidocaine HCl converted from crystalline form into amorphous form upon the HME and 3D printing processes. This amorphous dispersion explains the high aqueous solubility which is reflected as high release profile in short period.

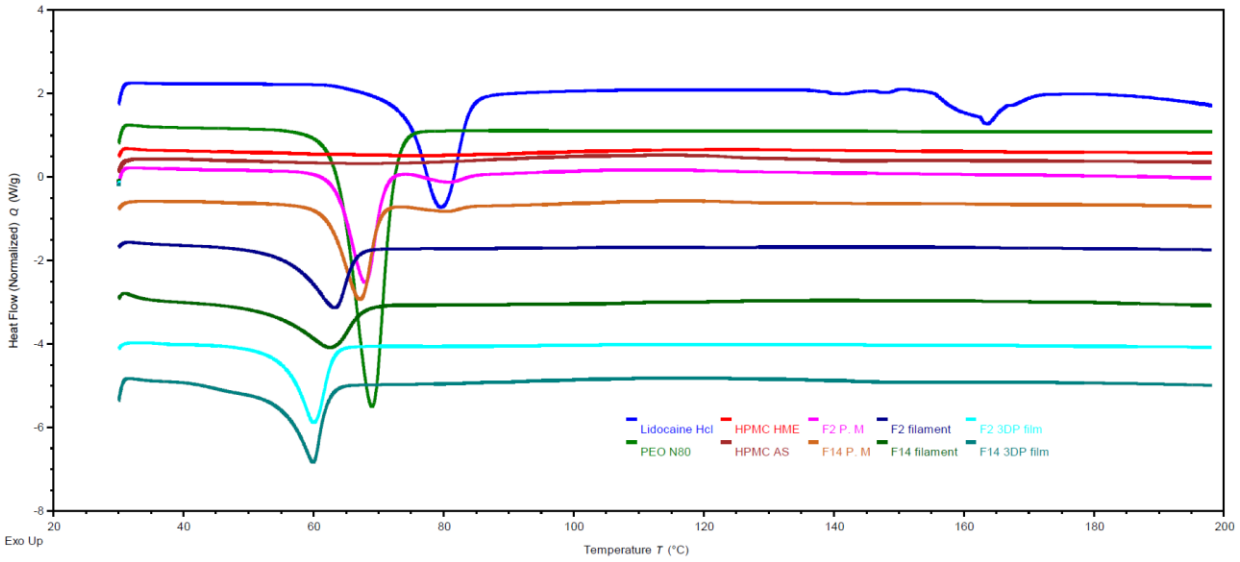


Figure 10 DSC Curves

### *In Vitro* Release

The release studies were conducted over 2 hours period where a sample withdrawn every 15 minutes in the first hour, then every 30 minutes in the second hour for F2 samples, the observed release was a raid release profile where all samples showed almost identical release behavior regardless of the infill shape and percent, where all samples released more than 85% 15 min then increased slightly up to the 30 min time point then plateaued at 90% until the end of the second hour. Table 7 and Figures 11 and 12 show F2 samples release profile.

Table 7 F2 Films Release

| | 100 Lines | | 70 Grid | | 40 Lines | |
|---|---|---|---|---|---|---|
| Time (min) | Release % | S. D | Release % | S. D | Release % | S. D |
| 0 | 0.0 | 0.00 | 0.0 | 0.00 | 0.0 | 0.00 |
| 15 | 87.5 | 4.91 | 90.9 | 1.84 | 91.5 | 0.85 |
| 30 | 90.6 | 1.04 | 91.1 | 2.07 | 91.4 | 1.00 |
| 45 | 90.6 | 1.05 | 91.5 | 1.13 | 91.1 | 0.87 |
| 60 | 90.6 | 1.13 | 91.3 | 1.04 | 91.2 | 1.06 |
| 90 | 90.5 | 1.15 | 91.3 | 1.00 | 91.0 | 1.13 |
| 120 | 90.5 | 1.19 | 91.0 | 1.01 | 90.3 | 1.47 |

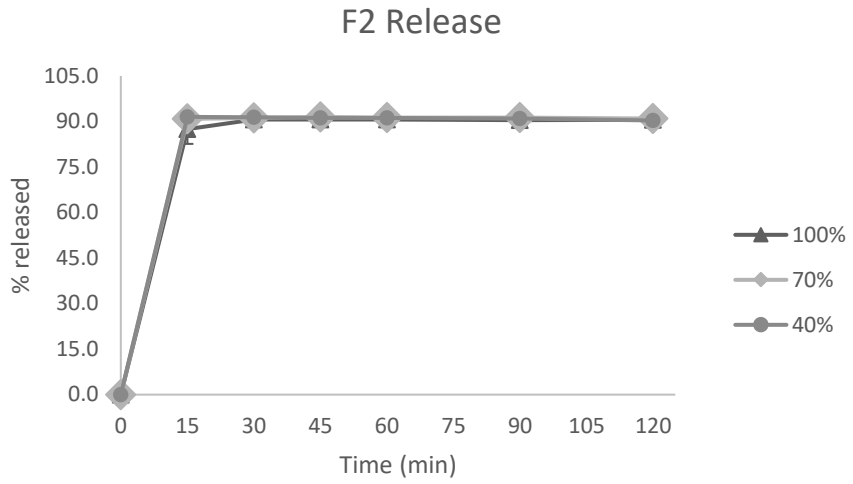


Figure 11 F2 Films Release Profile

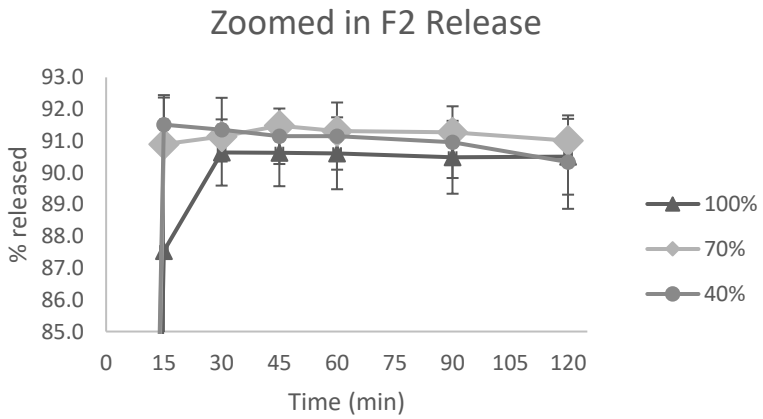


Figure 12 Detailed Release Profile of F2 films

Due to the rapid release observed in F2 samples within the first 15 min, the release behavior between time point 0 min and 15 min was investigated to compare it to the profile observed for F14, therefore two additional sampling time points that is 5 min and 10 min has been added in the F14 Release study. As Table 8 and Figures 13 and 14 shows, the release profile of F14 samples was similar to that observed in F2 but in earlier onset. Release of 95% of

all samples observed at the 5 min mark in F14 then increased to the maximum release amount at the 10 min mark then plateaued afterward to the end of the second hour instead of 15 min in F2 then increased slightly up to the 30 min time point then plateaued at  until the end of the second hour.

Table 8 F14 Films Release

| | 100 Grid | | 70 Lines | | 40 Grid | |
|---|---|---|---|---|---|---|
| Time (min) | Release % | S. D | Release % | S. D | Release % | S. D |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 5 | 97.83 | 9.76 | 94.42 | 5.22 | 97.73 | 4.43 |
| 10 | 101.36 | 11.64 | 95.51 | 6.35 | 97.94 | 4.36 |
| 15 | 101.86 | 11.87 | 95.59 | 6.54 | 97.90 | 4.28 |
| 30 | 101.86 | 11.84 | 94.88 | 7.09 | 97.85 | 4.34 |
| 45 | 101.86 | 11.80 | 95.34 | 6.71 | 97.72 | 4.31 |
| 60 | 101.71 | 11.75 | 95.28 | 6.51 | 97.66 | 4.34 |
| 90 | 101.60 | 11.75 | 95.18 | 6.60 | 97.58 | 4.29 |
| 120 | 101.72 | 11.73 | 95.06 | 6.59 | 97.45 | 4.35 |

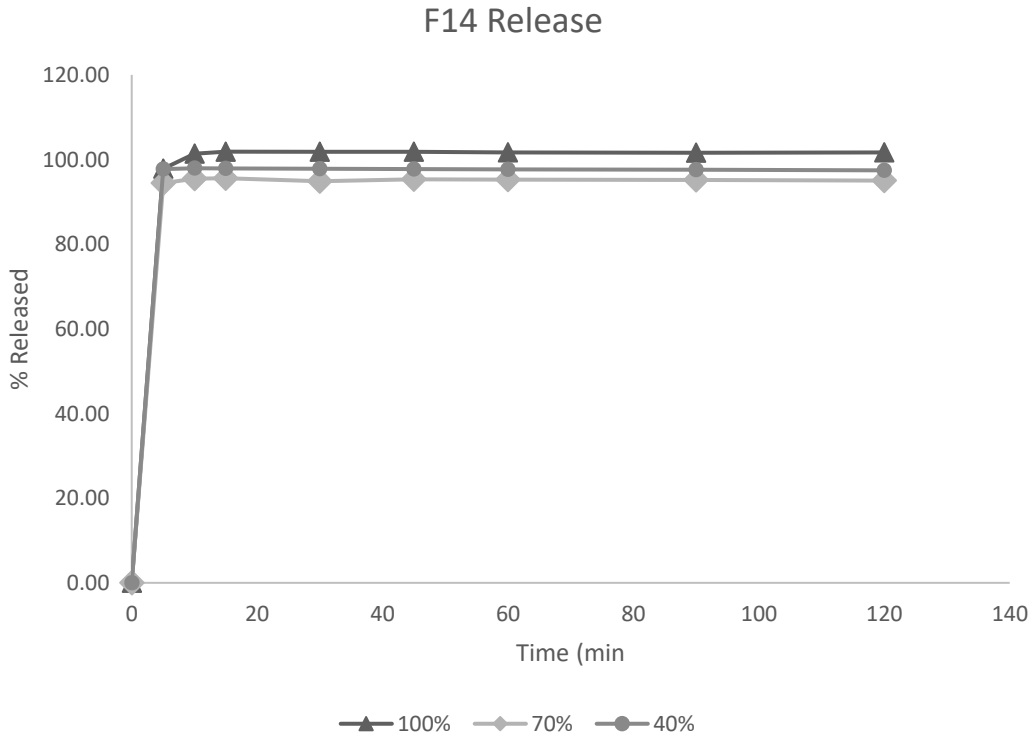


Figure 13 F14 Films Release Profile

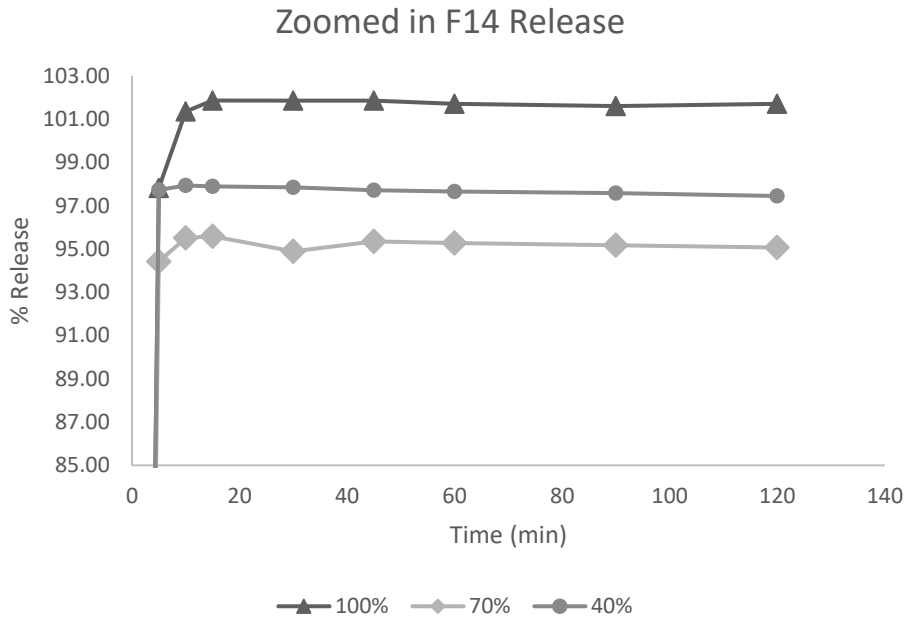


Figure 14 Detailed Release Profile of F14 films

**Film Strength**

The film strength is a mechanical feature that assessed to assure that 3D printed film shows enough durability during handling and shipping. Films strength observed to be proportional to the infill percent where films of 100% infill from both formulations showed the highest strength compared to the 70% and 40% infills. The higher the infill the stronger the film.

Table 9 3DP Films Strength

| n=5 | infill % | Strength (g) | Stiffness (g/Sec) |
|---|---|---|---|
| F2 | 40 | 287.796 | 152.474 |
| | 70 | 543.700 | 357.589 |
| | 100 | 1430.327 | 741.324 |
| F14 | 40 | 123.071 | 109.282 |
| | 70 | 178.457 | 112.131 |
| | 100 | 372.596 | 327.653 |

**Folding Endurance**

The results of the folding endurance test for the 3D printed films showed sufficient mechanical durability and elasticity of the finished pharmaceutical product. Three films of each infill from each formulation were folded until completely broken, it is worth to mention that the infill pattern of all films used in this test is the lines pattern. The results are depicted in Table 10 and Figure 15 below. The results suggest that as the higher the infill percent, the more durable and tolerant the film becomes. Which help in the patient's compliance issue steamed from the lack of physical flexibility.

Table 10 Folding Times to Break

| | 100% | 70% | 40% |
|---|---|---|---|
| F2 | 152 ± 31 | 173 ±19 | 135 ±11 |
| F14 | 149 ±25 | 131 ±22 | 54 ±10 |

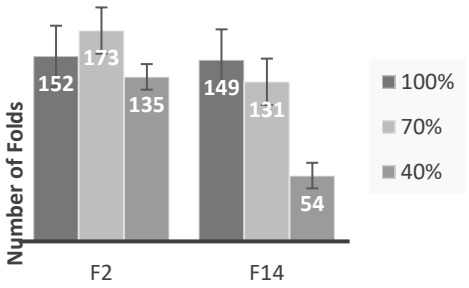


Figure 15 3DP films Folding Endurance

**Adhesion**

Samples adhesion was assessed over two stages of wetting, the first stage was after wetting the samples for 30 seconds in SSF, the second stage was after 5 minutes of immersing the samples in the SSF to simulate the wetting behavior in the oral cavity over the administration

period. As depicted in Table 11 and Table 12, F2 and F14 samples which were wetted for 30 sec, once wetted and fixed, they required four times the force (represented by the peak force) to detach the samples from the surface compared to the samples wetted for 5 min, however samples from both formulations in both stages showed similarity on the parameters of adhesiveness, and work of adhesion results, but the stringiness was four times higher in samples wetted for 5 min, because samples were hydrated due to the HPMC existence in the formulation (Patil, Tiwari, & Repka, 2016) that makes it softer and relatively pliable.

Due to the absence of a marketed, pharmaceutically equivalent, reference-product to compare the 3D printed films to, these results of adhesion will be used as the acceptance specification as well as the standard used in future studies.

Table 11 Adhesion Results After 30 sec of Wetting

| n=5 | Infill % | peak force (N) | Adhesiveness | work of adhesion (N.mm) | stringiness (mm) |
|---|---|---|---|---|---|
| F2 | 40 | 4.57 | 2.57 | 0.82 | 1.02 |
| | 70 | 4.86 | 2.14 | 0.68 | 1.17 |
| | 100 | 4.48 | 2.77 | 0.60 | 0.94 |
| F14 | 40 | 3.05 | 2.61 | 0.36 | 1.15 |
| | 70 | 4.09 | 2.81 | 0.57 | 1.55 |
| | 100 | 3.76 | 1.51 | 0.36 | 0.28 |

Table 12 Adhesion Results After 5 min of Wetting

| n=5 | Infill % | peak force (N) | Adhesiveness | work of adhesion (N.mm) | stringiness (mm) |
|---|---|---|---|---|---|
| F2 | 40 | 1.439 | 2.542 | 0.497 | 3.297 |
| | 70 | 1.932 | 2.352 | 0.843 | 4.12 |
| | 100 | 2.807 | 1.934 | 1.267 | 4.453 |
| F14 | 40 | 1.326 | 2.193 | 0.462 | 4.007 |
| | 70 | 1.616 | 2.438 | 0.552 | 3.136 |
| | 100 | 2.699 | 2.099 | 0.873 | 0.84 |

# CHAPTER 4

# CONCLUSION

Mucoadhesive 3D printed lidocaine film were successfully produced using HME extruded Filament and FDM 3D printer. The films characterization yielded satisfactory results in term of lidocaine content and its release from the film in SSF. Furthermore, the mechanical criteria of the films met established conditions. The films showed sufficient strength and good adhesion profile over to different stages of wetting by SSF.

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# VITA

## Personal Information

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| FIRST NAME / SURNAME | Mohammed Y. Alyahya |
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## Professional Work Experience

| | |
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| DATES | August 2017 - Present. |
| POSITION | Demonstrator at the Department of Pharmaceutics. |
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| DATES | December 2013 - August 2017 (3 years and 9 months) |
| POSITION | Finished Pharmaceutical Product (FPP) Quality Assessor at Saudi Food and Drug Authority (SFDA). |
| RESPONSIBILITIES | As FPP quality assessor, I assess the submitted technical data related to the final quality of products seeking registration within SFDA, qualities such as Product development, Manufacturing processes and their validation, Impurities profile and stability of the product. |
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## Education and Training

| | |
|---|---|
| **DATES** | Aug 2016 - May 2018 |
| **QUALIFICATION AWARDED** | Master of Business Administration |
| **PRINCIPAL STUDIES** | Organizational Quality and Operations Management |
| **INSTITUTION** | Saudi Electronic University |

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| **DATES** | Feb 2015 - March 2015 |
| **QUALIFICATION AWARDED** | Certificate of Participation |
| **PRINCIPAL STUDIES** | Industrial Quality Control |
| **INSTITUTION** | Jazeera Pharmaceutical Industries |

| | |
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| **DATES** | 09 June 2012 - 25 July 2012 |
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| **PRINCIPAL STUDIES** | Hospital pharmacy management. |
| **INSTITUTION** | King Fahad Medical City, Riyadh, KSA |

| | |
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| **QUALIFICATION AWARDED** | Bachelor degree |
| **PRINCIPAL STUDIES** | Pharmaceutical Sciences |
| **INSTITUTION** | College of Pharmacy - King Saud University |

## Workshops and Courses

| | |
|---|---|
| **DATES** | 27 - 29 September 2015 |
| **WORKSHOP / COURSE TITLE** | Drug Product Stability & shelf-life. |
| **INSTITUTION** | The Centre For Professional Advancement (Spain) |

| | |
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| **DATES** | 5 - 7 January 2014 |
| **WORKSHOP / COURSE TITLE** | Understanding and Reviewing the Common Technical Document. |
| **INSTITUTION** | Pharmaceutical Training International (KSA) |

| | |
|---|---|
| **DATES** | 7 -10 April 2012 |
| **WORKSHOP / COURSE TITLE** | principles of Scientific Research |
| **INSTITUTION** | Medication Safety Research Chair (KSA) |

| | |
|---|---|
| **DATE** | 1 - 30 May 2011 |
| **WORKSHOP / COURSE TITLE** | Pharmaceutical Marketing |
| **INSTITUTION** | Eli Lilly and Company (KSA) |

| | |
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| **DATE** | 6 April 2011 |
| **WORKSHOP / COURSE TITLE** | Total Parenteral Nutrition workshop. |
| **INSTITUTION** | King Saudi University (KSA) |

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| **DATES** | 23 November 2011 |
| **WORKSHOP / COURSE TITLE** | Communication skills improvement |
| **INSTITUTION** | King Abdelaziz Centre For National Dialogue (KSA) |

## Conferences

- 1st international cardiovascular pharmacotherapy, conference and exhibition 12-13 /1/2010
- 2nd international pharmacoeconomics conference 2012
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## Skills and Competences

| | |
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| **LANGUAGE SPOKEN** | Arabic |
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## Extracurricular Activities

- Assistant researcher in the Medication Safety Research Chair at the college of pharmacy, KSU during the bachelor years.
- Head of Scientific committee in Medication Safety Research Chair 2012/2013.
- Vice President of the Pharmacy Club 2012/2013.
- Head Of scientific Committee in Pharmacy Club 2011 - 2013.
- Representative of the College of Pharmacy in the Medical Students Council 2011 - 2013.
- Representative of the College of Pharmacy in King Saud University president Council 2011 - 2013.
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