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CHARACTERIZATION OF DRUG-LOADED MILLED EXTRUDATE PARTICLES  
PRODUCED BY HOT MELT EXTRUSION TECHNOLOGY FOR  
DRY POWDER INHALERS

A thesis  
presented in partial fulfillment of requirements  
for the degree of Master of Science  
in the Department of Pharmaceutics and Drug Delivery  
The University of Mississippi

by

AHMED ALMOTAIRY

December 2018

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## ABSTRACT

The aim of the current investigation is to develop a sustained-release dry powder inhalation (DPI) formulation through continuous Hot Melt Extrusion (HME) process and see the impact of Sodium Bicarbonate (SB) and Mannitol (MAN) on the hydrophobic Eudragit RL PO (ERLPO) polymer. Ball milling and air-jet milling were utilized to have powder with a particle size range that is required for inhalation. Air-jet milled formulations showed promising particle size results compared to ball milled formulations. All solid-state characterization studies revealed no change on Theophylline (TH) crystallinity or occurrence of drug-excipient interactions in physical mixtures and formulations. X2 formulation released TH constantly over six hours and has an acceptable particle size range for a DPI, therefore, it was chosen as the best formulation. Due to the pores that created by SB during HME extrusion, X1 released about half of TH after 15 minutes and reached the maximum release on the eighth hour, nevertheless, its particles size was not appropriate for DPI. X3 had the most suitable particle size range for a DPI, however, it had no a sustained-release behavior and its release was the same as a pure TH. For future studies, X2 will be further investigated on Anderson Cascade impaction (ACI), a study that mimic the lung, and *in-vivo* study will be considered based on the ACI result.

## **DEDICATION**

This thesis is dedicated to my mother, Ms. Alanwar Almotairy, my father, Morisheed Almotairy, who may God accept his soul and grant him the heaven, and my brother Monir who guided, advised, and helped me a lot. Also, it is dedicated to my beloved wife Ms. Norah Almotairy, all my family, and everyone who helped me and guided me through my own journey to accomplish the master degree.

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Dr. Samir Ross and Dr. Mahavir Chougule who served on my committee, I am really thankful for their valuable suggestion and advices before, during, and after the defence time especially Dr. Chougule who guided me throughout some parts of my thesis.

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## 1. INTRODUCTION

The local drug delivery approach has been concern of researchers over decades especially the pulmonary drug delivery as a dry powder inhaler (DPI) [1]–[4]. Many researchers explored this new route to treat many local diseases such as respiratory infection, Tuberculosis and Cystic fibrosis, also administering Cyclosporine as an immune suppressive drug or Ibuprofen as a non-steroidal anti-inflammatory agent [4]–[8]. High bioavailability, fast onset of action, bypass liver metabolism, and absence of breath actuation and propellant have made DPI the most preferred lung formulation [3], [9]. On the other hand, the lung has a limited volume and that would be a problem for water-insoluble drugs, thus a water-soluble drug, Theophylline (TH), was chosen to be the model drug on this investigation due to its moderate solubility in water, which is 7.36 mg ml<sup>-1</sup> [10].

Theophylline (Figure 1) is a bronchodilator and has efficiency for treating asthma and chronic obstruction pulmonary disorder (COPD) [11]. Also, Barnes reported that at low doses in asthma and COPD diseases, TH shows immunomodulatory actions and Fredholm also noticed that theophylline improved corticosteroids anti-inflammatory property [12], [13]. However, TH has a narrow therapeutic window and adverse reactions on gastrointestinal and cardiovascular systems, therefore, preparing TH as an oral sustained-release tablet (as in the market right now) or a DPI formulation would help to minimize these problems [14], [15]. Moreover, M. Malamatarı et al., A. Alhalaweh et al., reported the crystallinity behavior of TH during the spray drying by different

solid-state characterization (thermal and non-thermal) methods and stated that TH tends to preserve its crystallinity even during the exposure to a high temperature [16], [17].

Hot-melt extrusion (HME) has gained a popularity among the pharmaceutical applications over the past forty years due to the ability to produce several versatile formulations. HME's ability derived from its advantages over the traditional pharmaceutical processing techniques which are including, but not limited to, continuous operation, solvent-free method, few processing steps, low cost, and the possibility for industrial scale-up [18], [19].

A fine solid crystal suspension (FSCS) is a term has been used recently by L. Lin et al. which combines two different techniques to produce a fine crystalline powder to be used as DPI [20]. The first technique was using HME to produce a solid crystal suspension (SCS) which the crystalline drug suspends in the crystalline excipient. This method showed a good physical stability and low hygroscopicity [21], [22]. The other one was using the air-jet milling technique to produce a fine particle size powder to be used for inhalation [20].

Mannitol (MAN) was chosen to play an important role in formulations and its concentration will be dominant to produce SCS while formulations were extruded and to improve the milling efficiency for having FSCS formulations. In addition, the good flow property of mannitol would improve the aerosolization performance of formulations and increase the drug release inside the lung after being mixed with the lung fluids due to its ability as a pore former [23], [24].

Eudragit® RL PO (ERLPO) has been used commonly in HME process. Due to its quaternary ammonium groups that act as salts, the permeability of this hydrophobic copolymer toward dissolution media increased and that makes it a good candidate to be in the sustained-release formulations [25]–[28].

The aims of this study were investigating the feasibility to produce FSCS formulations using the HME and two dry milling techniques (a ball milling and an air-jet milling) to get a DPI, studying the release profile of polymeric and non-polymeric FSCS formulations, and the possibility of producing light and porous particles using Sodium Bicarbonate (SB) during the HME process. Many reports used a polymer to produce a sustained-release powder for DPI by different processing techniques, therefore, Eudragit® RL PO (ERLPO) was utilized in some formulations by different concentrations to investigate if there is a release difference inside the limited lung fluids.

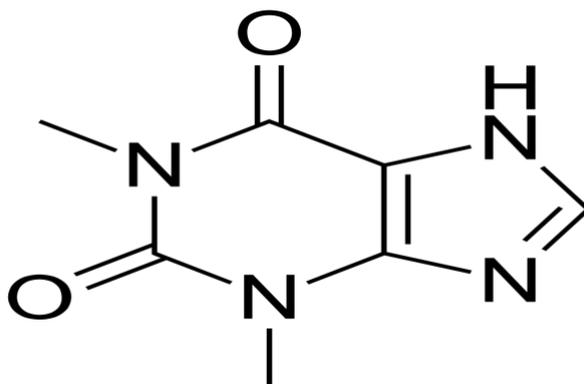


Figure 1: Theophylline Structure

## **2. MATERIALS AND METHODS**

### **2.1. Materials**

Anhydrous theophylline (TH) was purchased from Acros Organic (Thermo Fisher Scientific, NJ, USA). Pearlitol® 160 C (Mannitol) MAN was obtained as a gift sample from Roquette (1417 Exchange Street, P.O. Box 6647, Keokuk, IA 52632). Eudragit® RL PO (ERLPO) was kindly gifted by Evonik industries (Piscataway, USA). Sodium bicarbonate (SB) was purchased from Fisher Scientific (Hanover Park, IL, USA).

### **2.2. Methods**

#### **2.2.1. Hot Melt Extrusion**

The active pharmaceutical ingredient at different drug loads was mixed with ERLPO, SB and MAN (Table 1) using a V-shell blender (MaxiBlend™, GlobePharma, North Brunswick, NJ, USA) at 25 rpm for 15 min. The physical mixtures were extruded successfully using a co-rotating twin-screw extruder (11 mm Process 11™, Thermo Fischer Scientific, Karlsruhe, Germany) with standard screw design (Figure 2).

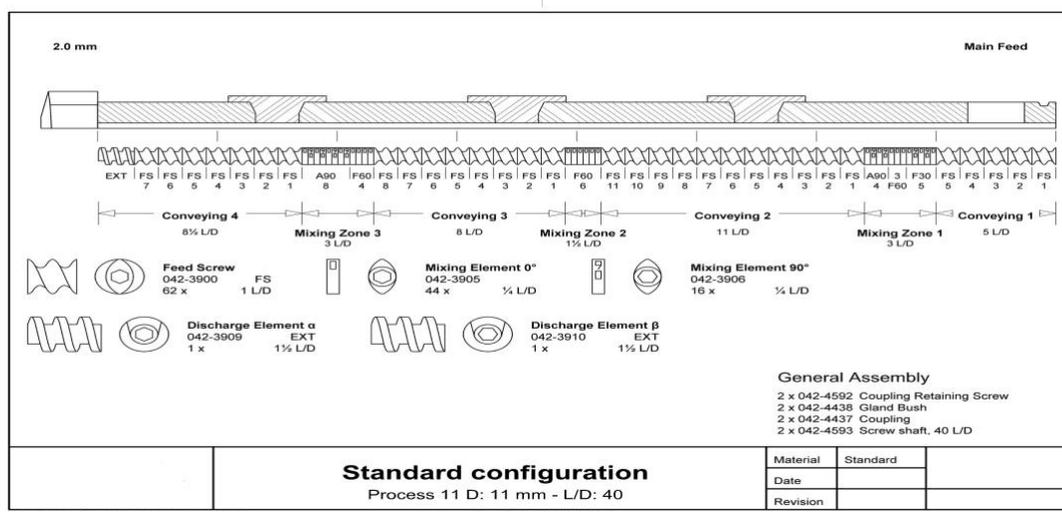


Figure 2: HME standard screw design

### 2.2.2. Preparing the DPI formulation

DPI formulations were prepared using two dry milling techniques. The first one was ball milling using (Mixer Mill MM400, Retsch GmbH & Co. Germany). 5 mg of each extruded formulation was placed in a 25-ml stainless steel milling jar and accompanied by 3 stainless steel balls (6 mm diameter each). The extrudates were milled for 30 min at 30-Hz oscillations. The second technique was using air-jet milling (Model 00 Jet-O-Mizer™ also known as Aljet mill, Fluid Energy, Telford, PA, USA).

### 2.2.3. Differential Scanning Calorimetry (DSC)

The thermal behavior of TH, ERLPO, and other excipients was studied by DSC 25, TA Instrument which was calibrated with indium. Samples (4–5 mg) were crimped in standard aluminum pans and sealed with the standard aluminum lid. After that, they were heated and scanned from 30 to 300°C at a heating rate of 20°C /min under a flow rate of 50ml/min of dry nitrogen atmosphere. An empty aluminum pan was placed as a reference.

#### 2.2.4. Power X-ray Diffraction (PXRD):

PXRD was performed using a Bruker D8 Advance (Bruker, Billerica, MA, USA) with a Cu-source and theta-2theta diffractometer equipped with a Lynx-eye Position Sensitive Detector. The generator was set to a voltage of 40 kV and a current of 30 mA. The samples were dispersed on a low background Si sample holder and compacted gently with the back of a metal spatula. The scan ran from 5° to 40° 2θ with a 0.05 step size at 3 s/step.

#### 2.2.5. Fourier Transform Infrared Spectroscopy (FT-IR)

FTIR analysis was conducted in the spectral range of 4000–650cm<sup>-1</sup> using Cary 660 and Cary 620 FTIR Microscopes (Agilent Technologies, Santa Clara, CA, USA). The bench was equipped with a MIRacle ATR (Pike Technologies, Fitchburg, WI, USA), that was fitted with a single bounce, diamond-coated ZnSe internal reflection element. FT-IR was performed to determine molecular interactions of pure TH and in the presence of SB, MAN and ERLPO in the formulations before and after applying high shear forces and elevated temperatures.

Table 1: Formulations composition, HME process parameters, and drug content

Formulations	TH %	MAN %	ERLPO %	SB %	Temperature °C	Screw speed (rpm)	Drug Content (%)
X1	30	40	25	5	160	150	99.8±0.4
X2	20	60	20	0	160	200	100.6±0.1
X3	20	80	0	0	160	200	100.2±0.2

### 2.2.6. Powder density and flow properties

The flowability of formulations was determined by measuring the bulk and tapped densities to calculate Carr's index (CI) and Hausner ratio (HR) (Table 2). The powder of each formulation was placed into a 25-mL measuring cylinder and the bulk volume was recorded, then the cylinder was tapped 100 taps manually and the new tapped volume was noted[14]. Based on preliminary experiments, 100 taps were enough to reach the maximum powder reduction. Then Carr's Index and Hausner ratio were calculated using the following equations:

$$CI = \left( \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \right) \times 100 \quad \text{Hausner ratio} = \frac{\text{tap density}}{\text{bulk density}}$$

Table 2: Formulation densities, Carr's index, Hausner ratio, and moisture content

Formulation	Bulk Density (g/cm <sup>3</sup> )	Tapped Density (g/cm <sup>3</sup> )	CI (%)	HR	Moisture content (%)
X1	0.34±0.04	0.46±0.03	25	1.33	2.49
X2	0.32±0.02	0.41±0.03	22.2	1.28	0.7
X3	0.3±0.01	0.36±0.02	16.6	1.2	0.68

### 2.2.7. Scanning Electron Microscopy (SEM)

The samples were placed on aluminum stubs held with a carbon adhesive film. Gold was used to coat the samples by a Hummer 6.2 sputtering system (Anatech Ltd., Battlecreek, MI, USA) in a high-vacuum evaporator. The surface morphology of every sample was analyzed by a scanning electron microscope (SEM) operating at an accelerating voltage from 1.0 kV to 5.0 kV (JEOL JSM-5600; JEOL, Inc., Peabody, MA, USA). FIJI/Image J software was used to record the pore diameter and study the impact of SB on pore formation before and after the milling process.

### **2.2.8. Moisture Content**

Moisture content was studied by evaluating loss on drying (LOD) using a halogen moisture analyzer balance (MB45 moisture analyzer, Ohaus, USA). The percentage of moisture was estimated by drying 1-2 g of each formulation at 105 °C for 10 min (Table 2).

### **2.2.9. HPLC Analysis**

Quantitative high-performance liquid chromatography (HPLC) was used as mentioned in USP 38 with an isocratic mode of elution (Waters Corp., Milford, MA, USA) equipped with an autosampler, UV/VIS detector and Empower software. The column was a reverse phase XTerra® C18 (5µm, 150 mm x 4.6 mm) was used to analyze theophylline at 280 nm wavelength. The mobile phase consisted of 92:7:1 % (v/v/v) of 0.01M sodium acetate trihydrate buffer: acetonitrile: glacial acetic acid pumped at a flow rate of 1 mL/min and the injection volume was 10µL. The samples were filtered using a 0.22µm filter (Millex® GV, Durapore® PVDF).

### **2.2.10. Drug Content**

An amount, that has 50 mg of TH, of each extruded formulation was dissolved in 50 ml water and TH concentrations were detected by HPLC system as mentioned previously on HPLC analysis section. The correlation coefficient of the calibration curve was 0.999 over a concentration range of 1-225 µg ml<sup>-1</sup>

### **2.2.11. Particle size distribution (PSD) by laser light diffraction**

PSDs were determined using a Sympatec Helos equipped with a Cuvette module (System-Partikel-Technik GmbH, Clausthal-Zellerfeld, Germany). Data were analyzed using the

Sympatec WINDOX software. The particle size distribution of each air-jet milled formulation was measured and particle diameters at the 10<sup>th</sup> (D<sub>10</sub>), 50<sup>th</sup> (D<sub>50</sub>), and 90<sup>th</sup> (D<sub>90</sub>) percentile were observed and used to calculate the span by the following equation:  $\text{Span}=(d_{90}-d_{10})/d_{50}$ . A lower span means a narrow size distribution (Table 3).

#### **2.2.12. Drug release-study**

Dissolution was performed for the extruded DPI formulations in phosphate-buffered saline (1 mL, pH 7.4) in dialysis bag and then placed into the phosphate buffer dissolution medium (37±0.5 °C, 100 rpm) using a dialysis bag with a molecular weight cut-off of 20,000 Da. To accomplish the sink conditions and the saturation solubility of TH, 300 mL of dissolution media was used and an exact amount was compensated during every sample withdrawn. The samples were withdrawn at predetermined time intervals over eight hours. The samples were suitably diluted and analyzed for theophylline content by UV spectrophotometry at 274nm wavelength[14].

### 3. RESULTS AND DISCUSSION

#### 3.1. Solid State Characterization

##### 3.1.1. DSC

The thermal behavior of TH, MAN, ERLPO, and SB was analyzed by DSC. The pure TH endothermic peak was observed at 275°C (Figure 3). The DSC results revealed the crystalline nature of TH in the extrudates and other excipients thermal stability during HME at the extrusion temperature (160°C), but PXRD is required to proof the crystallinity of TH. Ball and air-jet milling had no effect on the status of extruded formulations especially the crystallinity of MAN which was seen and noticed after the HME. The TH melting peak showed a change in its thermal behavior in the presence of MAN (Figure 4), it disappeared before and after the HME process, which is probably explained by the hypothesis that it dissolved in the MAN during extrusion [16]. MAN's endothermic peak was sharp and seen at 170°C in physical mixtures or extrudates.

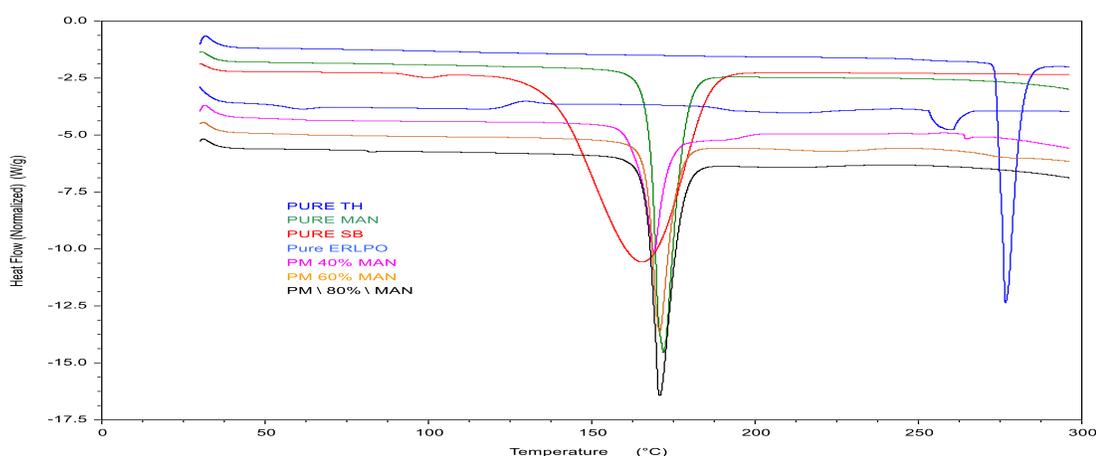


Figure 3: DSC thermal curves of pure TH, MAN, ERLPO, SB, and physical mixture

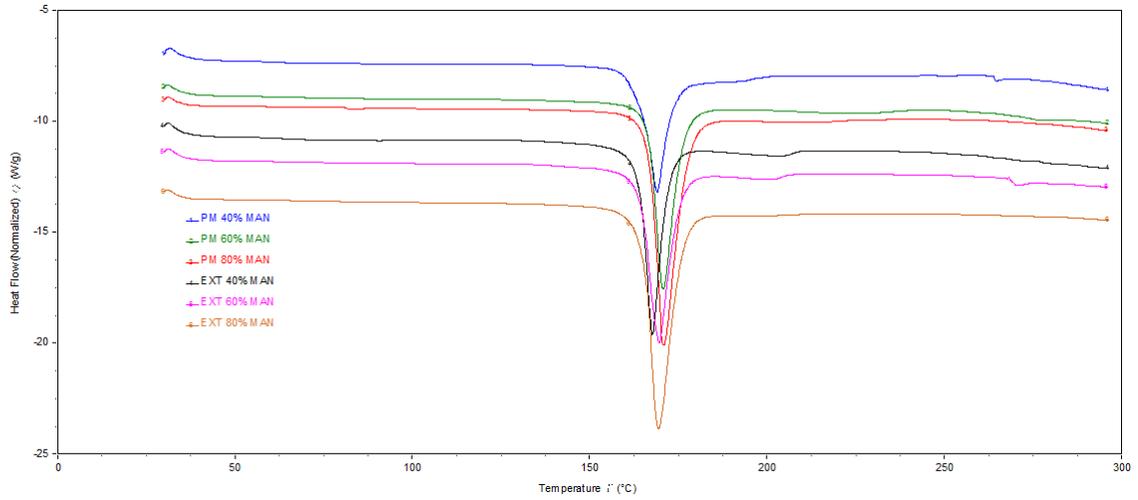


Figure 4: DSC thermal curves of physical mixtures and extruded formulations

### 3.1.2. PXRD

PXRD studies of pure TH and formulation showed the presence of all characteristic peaks of TH, thus, TH retained its crystalline nature after the exposure to a high temperature during the HME process (Figure 5).

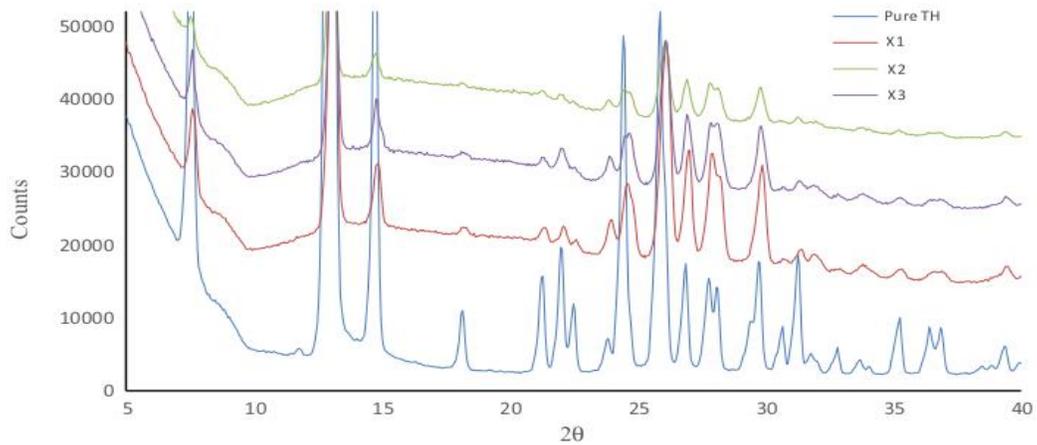


Figure 5: PXRD of pure TH and formulations

### 3.1.3. FT-IR

TH showed prominent wavenumbers at 1704, 1659, and 1560  $\text{cm}^{-1}$  [29]. At the first two wavenumbers, FTIR revealed the presence of C=O stretching vibration of carbonyl groups and the stretching vibration of imine group at 1566  $\text{cm}^{-1}$  of TH (Figure 1) and other excipients peaks in physical mixtures and all extruded formulations (Figure 6, Figure 7, and Figure 8) suggesting no interaction occurred.



Figure 6: FT-IR results of X1

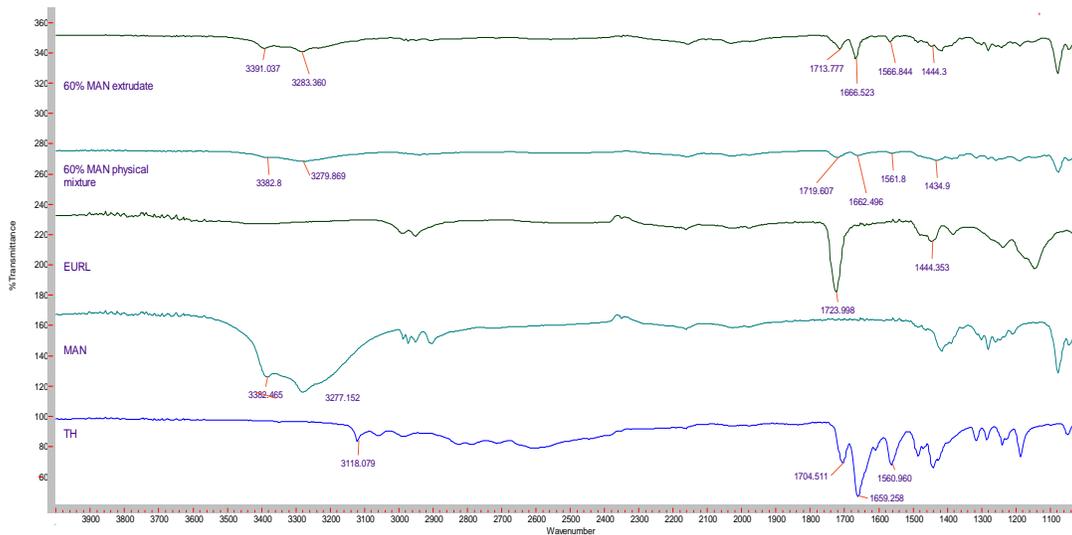


Figure 7: FT-IR results of X2

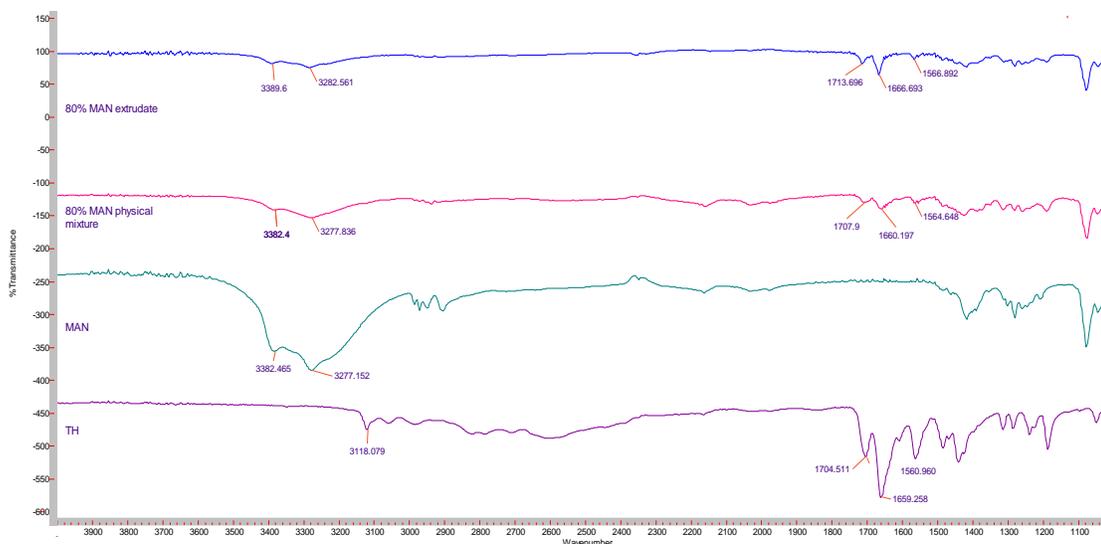


Figure 8: FT-IR results of X3

## 3.2. Characterization of Morphology and Particle size

### 3.2.1. SEM

A cross-sectional area of the extrudates was examined by SEM to see the effect of HME process and incorporation of Sodium Bicarbonate as a pore former. Figure 9 shows the image of formulation X1 and the resulted pores. The pores were varied in size and shape which may be an indication of places where SB distributed mostly inside formulations. On the preliminary study, it was noticed that incorporation of MAN led to enhance the screw speed performance which resulted in decreasing the residence time of formulations inside the HME and that led to decrease in the number of pores. SB did not get the efficient time to transfer into Sodium Carbonate and release all CO<sub>2</sub>. Furthermore, MAN helped to improve the torque situation during the process as its concentration in formulations increases and that because of its good flow property.

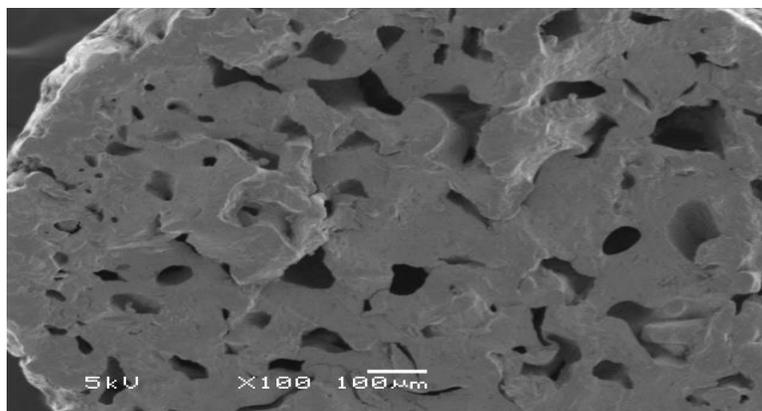


Figure 9: The SEM image of extrudate with Sodium Bicarbonate as a pore former

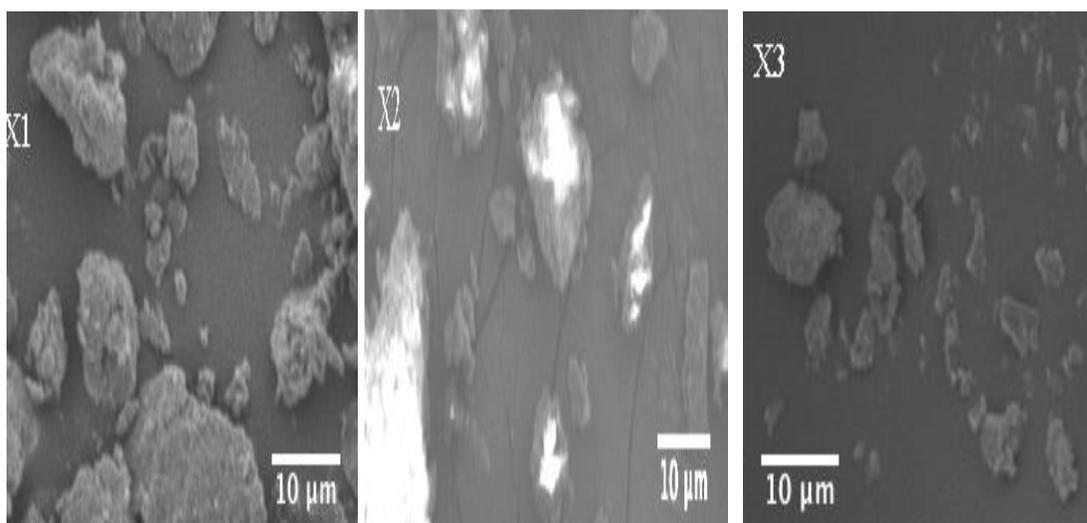


Figure 10: SEM images of ball milled formulations

The particle size and morphology of powder would have an influence on the dry powder inhaler performance in the lung [30]. Alhalaweh et al. and M. Malamatarı et al. pictured starting materials of Theophylline and mannitol by SEM and they described their shapes as needle-shaped particles and elongated particles, respectively [16], [17]. During the HME, materials liquefied, and final product was strands. The milling micronized these strands into a powder which were shaped differently than its origin as in Figure 10.

Figure 10 showed the formulations after micronized by the ball milling. Particles size differed from formulation to another and the range was approximately about 2-50 $\mu\text{m}$ . Also, it was noticed that as mannitol amount increased in the formulation the particle size decreased. Therefore, this change in size reduction supports the hypothesis that mannitol has a co-milling ability [31], [32].

Table 3: PSD parameters

Formulation	D <sub>10</sub> ( $\mu\text{m}$ )	D <sub>50</sub> ( $\mu\text{m}$ )	D <sub>90</sub> ( $\mu\text{m}$ )	Span
X1	12.77	34.25	45.39	0.9
X2	8.75	13.48	26.42	1.3
X3	5.57	6.25	11.16	0.8

### 3.2.2. PSD

The particle size distribution would be a key factor study on determining which is the efficient milling method in our study. The D<sub>50</sub> and D<sub>90</sub> of each formulation give an impression and a slight prediction about formulations' behavior on the Anderson cascade impaction (ACI) study which is considered a mimic for the lung system. The span of each formulation was a small number and that illustrates the narrow particle size distribution which means most particles were around the size of D<sub>50</sub>. X1 showed particles with bigger size than other formulations and that may be due to the low percentage of MAN in it, but its result was considered a better than the ball milling result when compare between them. X2 and X3 showed promising results especially when focusing on the D<sub>50</sub> which tells that the outcome percentages of half of the two formulations were within or near the acceptable range of DPI. Furthermore, X3 might be the promising formulation as a DPI due to its particles size which most of them were around the 6  $\mu\text{m}$ .

### **3.3. Moisture Content:**

X1 formulation was observed to absorb moisture more than other formulations and that related to sodium bicarbonate which has a hygroscopic nature [33], [34]. X2 has a water insoluble polymer and mannitol, which is only in X3, that has no a moisture uptake even at high relative humidity[35].

### **3.4. Drug release-study**

The formulations (X1 and X2) were expected to have a sustained-release behavior due to the presence of ERLPO, but the X3 was not (Table 1). X1 and X2 showed a variation on releasing TH at the first time point and that might be related to the low ERLPO's percentages that let TH dispersed incompletely inside their matrix (Figure 11). Therefore, some TH dissolved in mannitol and others dispersed on ERLPO. Furthermore, X1 exhibited a faster release on the first time point than other formulation by releasing 50% of TH and that could be the effect of pores which were generated by SB during the HME process. X2 showed the lowest release of TH content after 15 minutes among other formulations and reached its maximum release on the sixth hour. X3 and a pure TH were expected to behave in the same way and they were almost the same.

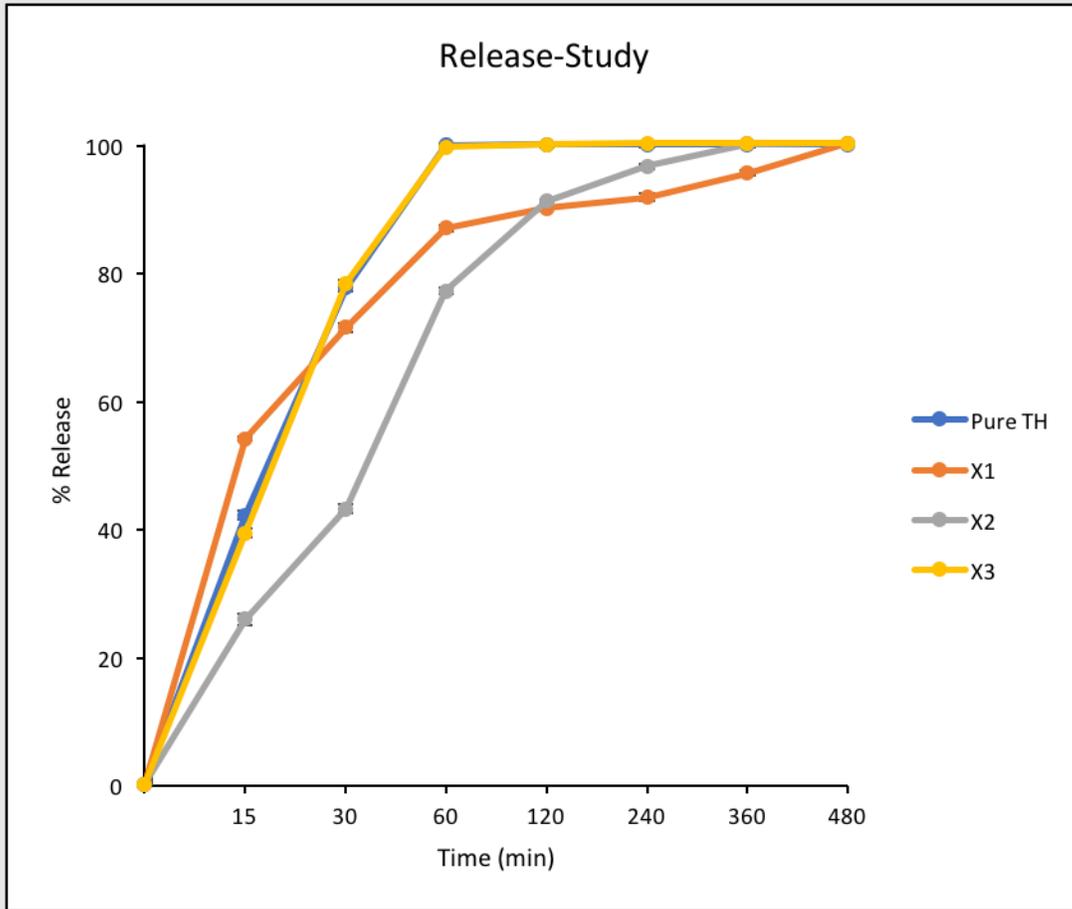


Figure 11: The release-study of all formulations

## BIBLIOGRAPHY

- [1] S. Onoue, H. Sato, Y. Kawabata, T. Mizumoto, N. Hashimoto, and S. Yamada, “In vitro and in vivo characterization on amorphous solid dispersion of cyclosporine A for inhalation therapy,” *J. Control. Release*, vol. 138, no. 1, pp. 16–23, 2009.
- [2] N. A. Beinborn, H. L. Lirola, and R. O. Williams, “Effect of process variables on morphology and aerodynamic properties of voriconazole formulations produced by thin film freezing,” *Int. J. Pharm.*, vol. 429, no. 1–2, pp. 46–57, 2012.
- [3] M. J. Telko and A. J. H. Dsc, “Dry Powder Inhaler Formulation,” pp. 1209–1227, 2005.
- [4] G. S. Zijlstra *et al.*, “Characterization of a cyclosporine solid dispersion for inhalation.,” *AAPS J.*, vol. 9, no. 2, pp. E190–E199, 2007.
- [5] Q. T. Zhou, S. S. Y. Leung, P. Tang, T. Parumasivam, Z. H. Loh, and H. K. Chan, “Inhaled formulations and pulmonary drug delivery systems for respiratory infections,” *Adv. Drug Deliv. Rev.*, vol. 85, pp. 83–99, 2015.
- [6] B. B. Eedara, I. G. Tucker, and S. C. Das, “Phospholipid-based pyrazinamide spray-dried inhalable powders for treating tuberculosis,” *Int. J. Pharm.*, vol. 506, no. 1–2, pp. 174–183, 2016.
- [7] B. K. Padhi, M. B. Chougule, and A. Misra, “Aerosol performance of large respirable particles of amikacin sulfate produced by spray and freeze drying techniques.,” *Curr. Drug Deliv.*, vol. 6, no. 1, pp. 8–16, 2009.
- [8] A. K. Yazdi and H. D. C. Smyth, “Carrier-free high-dose dry powder inhaler formulation of ibuprofen: Physicochemical characterization and in vitro aerodynamic performance,” *Int. J. Pharm.*, vol. 511, no. 1, pp. 403–414, 2016.
- [9] P. Atkins, “Dry powder inhalers: an overview.,” *Respir. Care*, vol. 50, no. 10, p. 1304, 2005.
- [10] S. H. Yalkowsky, Y. He, and P. Jain, *Handbook of Aqueous Solubility Data*, vol. 2. 2010.

- [11] A. Markham and D. Faulds, "Theophylline. A review of its potential steroid sparing effects in asthma," *Drugs*, vol. 56, no. 6, pp. 1081–1091, 1998.
- [12] P. J. Barnes, "Theophylline," *Am. J. Respir. Crit. Care Med.*, vol. 188, no. 8, pp. 901–906, 2013.
- [13] S. L. Tilley, "Methylxanthines in asthma," *Handbook of Experimental Pharmacology*, vol. 200, pp. 439–456, 2011.
- [14] H. Salem, M. Abdelrahim, K. A. Eid, and M. Sharaf, "Nanosized rods agglomerates as a new approach for formulation of a dry powder inhaler.," *Int. J. Nanomedicine*, vol. 6, pp. 311–320, 2011.
- [15] M. Nadai *et al.*, "Lack of effect of aciclovir on metabolism of theophylline and expression of hepatic cytochrome P450 1A2 in rats.," *Biol. Pharm. Bull.*, vol. 30, no. 3, pp. 562–8, 2007.
- [16] M. Malamataris, S. Somavarapu, K. Kachrimanis, M. Bloxham, K. M. G. Taylor, and G. Buckton, "Preparation of theophylline inhalable microcomposite particles by wet milling and spray drying: The influence of mannitol as a co-milling agent," *Int. J. Pharm.*, vol. 514, no. 1, pp. 200–211, 2016.
- [17] A. Alhalaweh, W. Kaialy, G. Buckton, H. Gill, A. Nokhodchi, and S. P. Velaga, "Theophylline Cocrystals Prepared by Spray Drying: Physicochemical Properties and Aerosolization Performance," *AAPS PharmSciTech*, vol. 14, no. 1, pp. 265–276, 2013.
- [18] M. M. Crowley *et al.*, "Pharmaceutical applications of hot-melt extrusion: Part I," *Drug Dev. Ind. Pharm.*, vol. 33, no. 9, pp. 909–926, 2007.
- [19] M. Lu *et al.*, "Application of hot melt extrusion for poorly water-soluble drugs: limitations, advances and future prospects," *Curr. Pharm. Des.*, vol. 20, no. 3, pp. 369–387, 2014.

- [20] L. Lin *et al.*, “Development of fine solid-crystal suspension with enhanced solubility, stability, and aerosolization performance for dry powder inhalation,” *Int. J. Pharm.*, vol. 533, no. 1, pp. 84–92, 2017.
- [21] M. Thommes, D. R. Ely, M. T. Carvajal, and R. Pinal, “Improvement of the dissolution rate of poorly soluble drugs by solid crystal suspensions,” *Mol. Pharm.*, vol. 8, no. 3, pp. 727–735, 2011.
- [22] E. Reitz, C. Vervaet, R. H. H. Neubert, and M. Thommes, “Solid crystal suspensions containing griseofulvin-Preparation and bioavailability testing,” *Eur. J. Pharm. Biopharm.*, vol. 83, no. 2, pp. 193–202, 2013.
- [23] J. E. Kim, S. R. Kim, S. H. Lee, C. H. Lee, and D. D. Kim, “The effect of pore formers on the controlled release of cefadroxil from a polyurethane matrix,” *Int. J. Pharm.*, vol. 201, no. 1, pp. 29–36, 2000.
- [24] N. N. Mohammed *et al.*, “KluceI™ EF and ELF polymers for immediate-release oral dosage forms prepared by melt extrusion technology,” *AAPS PharmSciTech*, vol. 13, no. 4, pp. 1158–1169, 2012.
- [25] W. Zheng, M. Cerea, D. Sauer, and J. W. McGinity, “Properties of theophylline tablets powder-coated with methacrylate ester copolymers,” *J. Drug Deliv. Sci. Technol.*, vol. 14, no. 4, pp. 319–325, 2004.
- [26] Y. Zhu, N. Shah, A. Waseem Malick, M. Infeld, and J. McGinity, “Controlled release of a poorly water-soluble drug from hot-melt extrudates containing acrylic polymers,” *Drug Dev. Ind. Pharm.*, vol. 32, no. 5, pp. 569–583, 2006.
- [27] L. Saerens, L. Dierickx, B. Lenain, C. Vervaet, J. P. Remon, and T. De Beer, “Raman spectroscopy for the in-line polymer-drug quantification and solid state characterization

- during a pharmaceutical hot-melt extrusion process,” *Eur. J. Pharm. Biopharm.*, vol. 77, no. 1, pp. 158–163, 2011.
- [28] B. K. Almutairy *et al.*, “Development of a floating drug delivery system with superior buoyancy in gastric fluid using hot-melt extrusion coupled with pressurized CO<sub>2</sub>,” *Pharmazie*, vol. 71, no. 3, pp. 128–133, 2016.
- [29] A. Nokhodchi, O. N. Okwudarue, H. Valizadeh, and M. N. Momin, “Cogrinding as a Tool to Produce Sustained Release Behavior for Theophylline Particles Containing Magnesium Stearate,” *AAPS PharmSciTech*, vol. 10, no. 4, pp. 1243–1251, 2009.
- [30] W. Kaialy, H. Larhrib, G. P. Martin, and A. Nokhodchi, “The effect of engineered mannitol-lactose mixture on dry powder inhaler performance,” *Pharm. Res.*, vol. 29, no. 8, pp. 2139–2156, 2012.
- [31] H. KUBO, T. OSAWA, K. TAKASHIMA, and M. MIZOBE, “Enhancement of Oral Bioavailability and Pharmacological Effect of 1-(3,4-Dimethoxyphenyl)-2,3-bis(methoxycarbonyl)-4-hydroxy-6,7,8-trimethoxynaphthalene (TA-7552), a New Hypocholesterolemic Agent, by Micronization in Co-ground Mixture with D-Mannitol,” *Biol. Pharm. Bull.*, vol. 19, no. 5, pp. 741–747, May 1996.
- [32] Y. Takahata, H. Nishioka and T. Osawa, “Micronization of poorly water soluble drug to submicron size by mixing grinding with low-molecular water-soluble crystalline additives,” *Funtai to Kogyo*, vol. 24, pp. 53–59, 1992.
- [33] W. Y. Kuu, R. Chilamkurti, and C. Chen, “Effect of relative humidity and temperature on moisture sorption and stability of sodium bicarbonate powder,” *Int. J. Pharm.*, vol. 166, no. 2, pp. 167–175, 1998.
- [34] S. C. S. Rocha and J. F. Nunes, “Agglomeration of Sodium Bicarbonate in Vibrofluidized

Bed: Process Analysis and Evaluation of CO<sub>2</sub>Release,” *Dry. Technol.*, vol. 30, no. 11–12, pp. 1332–1341, 2012.

- [35] R. C. Rowe, P. J. Sheskey, and M. E. Quinn, *Handbook of Pharmaceutical Excipients*, 6th editio. London, Chicago: Pharmaceutical Press, 2009.

## **VITA**

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