Spray Drying of Cocrystals for Engineering Particle Properties

Diploma Work in Chemical Engineering

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Abstract

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The goals of this work were to combine crystal and particle engineering in a single step using spray drying and improve particle properties that can potentially minimize the need for coating agents. Specific aim was to prepare and characterize theophylline cocrystal particles intended for inhalation using by spray drying. Theophylline is a bronchodilator used in the treatment of asthma and is used as a model drug in this study. Theophylline cocrystals with citric acid, flufenamic acid and saccharin were chosen as model systems. The solubilities of different components of cocrystals in different solvents were determined to get an idea of the stability landscape of cocrystals. Thereafter, the cocrystals were prepared by slurry crystallization method. The cocrystal particles from similar solutions were prepared using spray drying. The processing variables are carefully chosen for optimal particle engineering. The resulting solids were subjected to different characterizations such as particle size analysis, tap density and bulk density analysis and new generation impactor studies.

Theophylline cocrystals were successfully obtained by both slurry crystallization and spray drying methods. Despite rapid drying, spray dried particles were predominantly crystalline with a particle size and other attributes suitable for inhalation. However, the process yields were low due to adhesion to cyclone walls. The impactor results indicated a decent aerosolization performance of the spray dried particles in pure and when blended with lactose.

The cocrystal particles with interesting properties suitable for inhalation application can be prepared in one step using spray drying. The mechanisms behind reasons for adhesion of cocrystal particles should be further elucidated.

Key words: spray drying, cocrystals, cocrystallization, coformers, particle engineering, design of experiments, inhalation, theophylline, citric acid, flufenamic acid, saccharin.
Abbreviations

AC acetone
API active pharmaceutical ingredient
CA citric acid
CFC chlorofluorocarbon
COPD chronic obstructive pulmonary disease
DoE design of experiments
DPI dry powder inhaler
DSC differential scanning calorimetry
EtOAc ethyl acetate
EtOH ethanol
FFA flufenamic acid
FPD fine particle dose
FPF fine particle fraction
GSD geometric standard deviation
HFA hydrofluoroalkane
IGC inverse gas chromatography
MDI pressurized metered-dose inhaler
MeOH methanol
MMAD mass median aerodynamic diameter
M<sub>W</sub> molecular weight
NGI next generation impactor
PSD particle size distribution
PXRD powder X-ray diffraction
RT room temperature
SAC saccharin
SEM scanning electron microscope
<sub>T</sub><sub>G</sub> Glass transition temperature
TGA thermogravimetric analysis
THF theophylline
<sub>T</sub><sub>m</sub> melting temperature
UPLC ultra performance liquid chromatography
VMD volume mean diameter
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1. Introduction

The increased occurrence of pulmonary diseases such as asthma, chronic obstructive pulmonary disease (COPD), anesthesia, cystic fibrosis and infections makes the delivery of pulmonary drugs essential [1]. Within pulmonary drug delivery, there are many advantages with inhalation therapy compared to other delivery systems such as oral therapy and injection therapy. These advantages can be summarized by lower dosages, reduced unwanted side effects, lack of pain for example with injections and quick drug effects due to the large absorption surface and lack of first pass metabolism [1].

The primary delivery systems in pulmonary drug delivery include pressurized metered-dose inhaler (MDI), dry powder inhaler (DPI) and nebulizer. MDIs utilize suspensions, emulsions and solutions for inhalation and are in need of propellants such as hydrofluoroalkane (HFA) and chlorofluorocarbon (CFC), the latter is no longer used in Sweden. Nebulizers are on the other hand based on continuous atomization of a drug solution or suspension. They are most suitable for hospital use and are driven ultrasonically or by compressors. However, DPIs are widely used and are portable, inexpensive and fuel-free [1]. While drug particles from MDIs or nebulizers are usually placed in solution or suspension, DPI drug particles are delivered as powders. Dry powders are known to be less complex when formulated due to better stability than liquid dispersed systems. Therefore, the use of DPIs is beneficial in the delivery of many different drug particles to the pulmonary regions [2].

DPI powders come as either single-dose or multi-dose packaging. The powder consists of active pharmaceutical ingredient (API) alone or API with excipients to enhance powder properties and facilitate physical stability and dose adjustments. For the formulation to be most favorable, certain variables such as particle size, particle shape, surface energy, density, crystallinity and stability must meet the requirements. Consequently, the availability of successful particle formation techniques is of great importance for improving the particle properties of selected drug candidates. The most common techniques used for engineering particle properties include micronization, direct controlled crystallization, spray drying, spray freeze drying, particle formation from liquid dispersion systems, supercritical fluid processing and particle coating [3]. Naturally, each of the above mentioned techniques has its specific applications with merits and limitations. However the focus in this project will be on spray drying for the fact that particle engineering through spray drying is the major field of study at the moment.
1.1 Dry powder inhalers

DPIs are one of the most popular choices for inhalation devices and have a great frequency of use among patients, Figure 1. DPIs are based on three components which are the formulation, the metering system, and the aerosol dispersion mechanism [2]. For best inhalation performance, the drug formulation, the inhaler device, the metering system and the patient's inhalation technique need to be optimal [1][4]. Some of the drawbacks that are associated with DPIs are the fact that these devices are flow dependent i.e. de-aggregation through the patient's inhalation is required to release drug particles to the alveoli. Also, dry powders tend to be sensitive to moisture. Dispersion from DPIs is controlled by the interparticulate forces, the dispersion forces produced by the DPI and the deposition forces in the airways [5]. Also, breathing techniques and inhaler design affect penetration and deposition in the airways as well. The optimal DPI devices should permit an air flow rate of about 30 L/min through the device and deliver drug particles with ideal aerodynamic size [5].

Figure 1: An example of dry powder inhaler, Turbuhaler®

1.1.1 Dry powder formulations

Dry powder has lately become more common due to the prohibition of aerosol propellants (freon) and better drug deposition in the lungs. Dry powder inhalation products are usually made by combining micronized drug particles (2-6 µm) with larger carrier particles. Carrier particles have the function of improving powder flowability and preventing the small micronized drug particles from cohesion and aggregation [1]. The smaller drug particles in the powder mix adhere to the larger carrier particles by interactions such as van der Waals, capillary forces or electrostatic and mechanical interactions to form ordered units, this kind of mixtures is called ordered or interactive mixture, Figure 2 [5]. The active pharmaceutical ingredient adheres to the carrier particles to later detach in the lungs during inhalation as a result of the produced air flow [4]. Carrier particles, just like drug particles, must meet the requirements in terms of physicochemical stability, biocompatibility and being inert and cost-effective [1]. Lactose monohydrate is frequently used as a carrier because of its desirable powder properties. Besides mixing with carrier particles, granulation can also be attained to enhance powder flowability and dispersion thus dosing precision. Granulation is generally accomplished by adding
water at suitable temperature for the activation of the binder in the mixture. The granulates should, as in ordered mixtures, de-aggregate when coming out of the inhaler.

![Figure 2: API (blue) and carrier particles forming ordered mixture.](image)

1.1.2 Excipients

Generally, the function of excipients in a drug formulation is to improve drug properties such as physicochemical, mechanical and pharmaceutical properties [5]. One of the reasons why dry powders are favorable is the need for limited excipients in the formulation. In DPI formulations, excipients are used as carrier particles to create bulk and reduce drug cohesiveness by filling the high energy sites on the surface of the particles [5].

Lactose is a widely used carrier in the DPs due to its well-studied toxicity profile and good physicochemical stability. In addition to that, it has adequate powder properties and is cost-effective. Among the two existing isomers (α-lactose and β-lactose) of lactose, α-lactose monohydrate is the most common form in inhalation drugs [1][4]. Other carrier particles that are relevant in inhalation drug applications are glucose, mannitol, sorbitol, erythritol, trehalose, hydroxyapatite, cyclodextrins, dextrose, maltose, maltitol and xylitol [1]. These have been investigated in DPI formulations and some of them were found to be more successful than lactose when combined with specific inhalation drug compounds [1].
1.2 Spray drying

Spray drying is a scalable and well-known method for particle engineering. This technique is used for producing dry powder from solutions, emulsions and suspensions. The method is ideal for drying thermally sensitive materials such as proteins and peptides in pharmaceuticals and foods. The spray dried product is expected to fulfill specific quality standards in terms of particle size distribution, residual moisture content, physical purity, particle morphology, bulk density and surface energy [6][7]. The spray drying process involves the pulverization of a liquid into a spray of small drops and exposing these small drops to hot air in a drying chamber, the solvent evaporates quickly leaving behind solid particles. The process consists of four sequential stages which are: atomization of the resulting solid into a spray nozzle, spray-air contact, evaporation of the sprayed droplets and collection of the solid product. Processing conditions are selected according to the desired properties of the product and powder requirement [7]. The solid product is then separated mostly by either a cyclone or a filter bag, Figure 3 [8].

![Figure 3: Schematic picture on the spray-drying process](image)

1.2.1 Spray drying applications

The pharmaceutical applications of spray drying go back to nearly 50 years ago. The technique was first applied for the preparation of solids as a midway processing step in lactose processing [9]. Spray dried lactose was used mainly as an excipient for granulation and compression [9]. Today, spray drying is used in many applications including particle engineering and protein stabilizing in order to create and optimize emerging drug delivery systems [8]. Additional spray drying applications in the
pharmaceutical field include the production of APIs, dissolving tablets, microspheres, nanoparticles and liposomes [9].

![Mini spray dryer B-290 from Büchi.](image)

**Figure 4:** Mini spray dryer B-290 from Büchi.

### 1.2.2 Processing parameters

Typically, the particles generated from a spray drying process are solid, low-density amorphous particles, but through varying the processing conditions, particle properties can be modified [3]. To optimize product quality, processing conditions such as drying temperature, air flow and atomization pressure are changed. Using a Büchi Mini Spray Dryer allows altering a number of parameters including inlet temperature, air flow rate, pump speed rate, aspirator suction rate in addition to the concentration of the solution being spray dried and the choice of solvent [10]. Specific changes in processing variables lead to specific particle modifications. For preparing spray-dried powders for inhalation, it is valuable to use atomizers that produce suitable droplet size in the desired particle size range [11]. Factors like feed rate, atomization airflow and feed concentration also have an impact on particle size [3]. The size of the particles increases with increasing inlet drying temperature and feed rate and decreases with increasing airflow rate [3].

According to literature, increasing the drying airflow rate leads to decreasing moisture content and the higher the inlet temperature, the larger the heat gradient between the droplets and the drying air. Decreasing the aspirator rate leads to lower moisture content due to the longer dwelling time for the material in the drying chamber [3]. The process yield increases with increasing inlet air temperature, increasing aspirator rate and decreasing feed solution rate [3][12].
1.2.3 Particle engineering

The purpose of particle engineering is to design particles with advantageous features for optimal drug delivery and bioavailability. These features include suitable particle size with a narrow size distribution and high dispersibility for controlling the drug release [13]. Successful particle engineering leads to less industrial complexity and provides lower costs and trivial environmental impact [13]. With spray drying, inhalation aerosols without excipients can be prepared with adequate flowability and dispersibility. Preparing cocrystals with a variety of excipients makes the technique more responsive to particle engineering [13]. However, process parameters need to be optimized thoroughly in order to obtain desirable particle properties [10]. Knowing how these process parameters impact on the physicochemical properties of the product is a key in particle engineering and drug development [10].

1.2.4 Particle formation mechanism

The particle formation mechanism contains multiple steps as the droplets come into contact with hot air and convert into solid powder. To begin with, the droplets must be regulated by the temperature of the surroundings near the nozzle. At this stage, the type of atomizer is the most important variable for the initial droplet formation [9]. The second stage begins when the droplets have reached equilibrium during evaporation into the gas flow. Under constant rate of drying, the evaporation rate depends on the energy that is transmitted to the droplets [9].

The next stage falls when a fraction of the solvent has been evaporated and the evaporation rate is altered due to the higher density of the droplets. During this phase of falling rate period, the droplet surface begins to shape itself as a solid shell that may be either amorphous or crystalline. Particle formation mechanism is complicated and relies on several aspects such as initial droplet size, feedstock concentration, evaporation rate and particle physicochemical characteristics [9].

Many scientists turn to droplet evaporation rate and diffusion in solutes to understand the different mechanisms of particle formation [15]. For non-hollow particles, the droplet reduces in size and the dissolved substance migrates to the center of the droplet due to solvent evaporation [15]. Therefore, after saturation, solidification of the particles is attained [15]. For hollow and porous particles, evaporation is initiated earlier and the system is quickly full of precipitating dissolved substance [15]. A solid shell is immediately formed at the surface of the droplet prior to complete drying [15]. Because of the facts that the diffusion of dissolved substances is limited in pharmaceutical applications and evaporation is significantly faster than the diffusion rate, pharmaceutical particles tend to develop pores and become hollow [15].
1.3 Cocrystals

1.3.1 Cocrystal definition

Cocrystals can be defined as crystalline materials of more than one component in definite stoichiometric amounts, attached via non-covalent interactions; van der Waals, π–π stacking interactions, electrostatic interactions, halogen bonding and most importantly hydrogen bonding [7][16][17]. Cocrystal elements are neutral molecules that are solid at ambient temperature [16]. If one of the components has a pharmaceutically active nature, they are considered as pharmaceutical cocrystals. Moreover, the non-pharmaceutically active component must have a non-toxic profile without any adverse side effects [17][18]. Since the formation of cocrystals does not involve the formation of new covalent bonds, the pharmacological properties of the starting material shall not be changed. But the fact that the cocrystal structure is different from the original crystals, leads to different physical properties.

1.3.2 Cocrystal formers

The main demand for a coformer is pharmaceutical and general safety. Examples for pharmaceutical cocrystal formers that are used to co-crystallize with API include carboxylic acids, amides, carbohydrates, alcohols and amino acids [16]. Different types of carboxylic acids such as oxalic acid, glutaric acid, citric acid and maleic acid have been investigated as cocrystal formers. Hydrogen bond donors and acceptors in carboxylic acids allow for hydrogen interactions to take place [16].

1.3.3 Cocrystal design

There are some empirical cocrystal design rules that have been discussed in the recent years. These observed conclusions bring up the subject of intermolecular interactions as a key for cocrystal design. Hydrogen bonds are one of the most important intermolecular interactions in cocrystals. Hydrogen interactions in cocrystals are held together by certain hydrogen bond patterns called synthons. Synthons are in general categorized into two groups: homo- and heterosynthons [16]. Homosynthons occur between similar functional groups while heterosynthons are formed between different functional groups, Figure 5.
1.3.4 Cocrystallization techniques

Pharmaceutical cocrystal formation is a promising way to change the solid state properties of a drug substance to optimize drug properties i.e. improve stability, flowability, solubility and bioavailability [18]. For that reason, pharmaceutical cocrystals can play a major role in the future of drug development. Currently, several common cocrystallization strategies are discussed by the scientific community worldwide. Cocrystal screening and preparation strategies can be divided into two main categories; solvent-based and solid-based. Solvent-based techniques include slurry conversion, evaporation, cooling and anti-solvent addition while co-grinding and crystallization from the melt belong to the solid-based techniques [17]. Recently, it has been discovered that spray drying can be used to prepare pharmaceutical cocrystals [6].

1.3.5 Cocrystal phase diagrams

Ternary phase diagrams, Figure 6, are graphical symbolization to describe the physical composition of three-component systems. The three involved species in the composition are dependent on each other in stoichiometry and physical state. Liquid-based cocrystal systems are usually described by ternary phase diagrams where each axis of the triangle represents one of the ingredients. The eutectic points (E1 and E2) in the diagrams represent the equilibrium of two coexisting solid phases with a liquid phase. The regions between these points are defined as the thermodynamically stable areas of the cocrystals [7]. For congruently saturating systems, where the solubility profile of cocrystal component A and cocrystal component B in a given solvent is similar, the diagram looks symmetrical. In the case of incongruently saturating systems, the phase diagram looks asymmetrical due to the different solubilities for the cocrystal components. The main difference between congruently and incongruently saturating cocrystal systems is that congruently saturating cocrystals are thermodynamically stable when slurried in a congruent solvent, while incongruently saturating
cocrystals undergo transformation in incongruent solvents [7]. It is also important to know that a cocrystal system that dissolves congruently in one solvent does not necessarily have to dissolve congruently in other solvents [19].

Figure 6: Phase diagrams for congruent and incongruent cocrystal systems.

Region 1 consists of a liquid phase containing the solvent and the dissolved cocrystal components A and B. In region 2, both liquid and solid component A exist while region 6 contains of liquid and solid component B. Thus these two regions comprise 2 different phases (liquid and solid) and 3 components (solution, component A and component B). Regions 3 and 5 involve liquid, cocrystal (A-B) and either component A or B. These two regions (3 and 5) include 3 different phases (solution, cocrystals and pure components) and clearly 3 components. Region 4 includes liquid and cocrystal (A-B). Establishing a phase diagram for a certain cocrystal is strongly dependent on determining the invariant points E1 and E2 where no external parameters impact on the existing system.

Gibbs phase rule describes equilibrium in systems with different phases in terms of numbers of degrees of freedom. The number of degrees of freedom according to the equation is:

$$ F = C - P + n $$

where C is the number of components in the system, P is the number of phases in equilibrium and n is the number of external parameters which is often represented by temperature and pressure, taking the number of 2. In systems of liquid and solid phases (cocrystal systems) where pressure impact is insignificant, temperature is the only external parameter that is represented by n. Consequently, Gibbs phase rule for cocrystal systems is described by:
The number of degrees of freedom, also the variance of the system, is the number of parameters in a system that can possibly vary independently, regions with the lowest degrees of freedom should be the easiest regions to control due to the fewer external parameters that impact on the system.

1.4 Cocrystal particle properties

Drug deposition depends on the inhaler design, particle size, particle charge, particle density and hygroscopicity along with patient-dependent factors; inhalation speed, tidal volume, inhalation technique and airways. Therefore, the development of API formulations demands great understanding of the drug's physical and chemical properties. To offer further understanding of the importance of these qualities, a discussion on particle properties is provided below.

1.4.1 Crystalline and amorphous materials

- **Crystallinity**

In drug formulations, crystalline material is more desired than amorphous material due to better chemical and physical stability, lower surface energy and lower hygroscopicity. However, crystalline powders can have poor water solubility which leads to reduced dissolution and poor bioavailability. Through crystal modification, several physical properties such as solubility, cell dimensions and bulk properties can be improved.

- **Glass transition temperature**

Amorphous materials do not exhibit a melting point but rather a glass transition temperature $T_g$ which is the temperature at which hard, brittle, "glassy" amorphous materials convert into soft rubber-like materials [20]. The glass transition temperature is a common tool used for identifying and characterizing amorphous solids. For amorphous solids, solubility is not a problem as amorphous materials are significantly more soluble than crystalline materials due to lack of long range order in amorphous materials. For the same reason, amorphous systems (with low $T_g$) suffer from stability issues that usually are not associated with crystalline systems. Typically, the particles produced from spray drying have amorphous characteristics, but in some cases even crystalline particles can be generated.
- **Melting point**

Melting point is a primary physical property and the temperature at which equilibrium occurs between the solid phase and the liquid phase. A lot of research has been done to explore the melting point of cocrystals starting from the original components i.e. the drug and the cocrystal former [16]. Melting point measurements can be achieved using a differential scanning calorimeter (DSC) which is a primary tool in thermal analysis. It can be used to generate information about amorphous and crystalline behavior to learn about crystallization temperature, glass transition temperature and melting temperature. This technique makes it possible to also see polymorph and eutectic transitions, curing and degree of cure, crystallization and re-crystallization, degradation, loss of solvents and chemical reactions [22].

### 1.4.2 Solubility and dissolution rate

Solubility and dissolution rate are the most important physical properties in the pharmaceutical branch as the bioavailability of a drug compound is dependent on these variables. The connection between solubility and dissolution rate is presented below by the Nernst–Brunner/Noyes–Whitney equation:

\[
\frac{dM}{dt} = \frac{D \cdot A}{h} (C_e - C_t) \quad \text{Equ. 1}
\]

where \(dM/dt\) is the dissolution rate, \(D\) the diffusion coefficient, \(A\) the surface area of the solid, \(h\) the thickness of the diffusion layer, \(C_e\) is concentration of the drug in solution at equilibrium and \(C_t\) concentration of drug in solution at time \(t\) [20]. In other words, the dissolution rate is dependent on the diffusion coefficient, the surface area, the diffusion layer and the concentration gradient.

Examples of conventional methods that are traditionally used to enhance solubility and dissolution rate of poorly water-soluble compounds are salt formation, solid dispersion, use of surfactants and particle size reduction. Pharmaceutical cocrystallization is a relatively novel method that can improve material solubility/dissolution rate. The cocrystal eutectic constants (\(K_{eu}\)) can be used to direct cocrystallization and predict cocrystal solubility [16].

### 1.4.3 Particle bulk properties

- **Surface energy**

Amorphous materials are usually more surface active than crystalline materials. Small particles (nanoscale < 1 \(\mu\)m in size) are cohesive/adhesive and tend to attach to each other or to other surfaces.
due to their high surface energy. For inhalation dry powders, adhesion/cohesion is found to be critical for the inhalation performance. Particle surface energy is strongly associated with adhesion/cohesion [20]. Spray dried particles tend to have fewer points of contact when compared to micronized particles, therefore cohesion is reduced, dispersibility is improved and aerodynamic behavior is better [20]. Inverse gas chromatography (IGC) is a sensitive technique used in the determination of surface properties of DPI and pMDI formulations.

- **Density**

Low-density porous particles have recently become more attractive to scientists due to their superior aerodynamic properties. The aerodynamic diameter of a particle is a function of particle size and density. Particles with low density have small aerodynamic diameters due to their reduced mass relative to their maintained equivalent volume diameter. It is acknowledged that porous particles (low density particles) interact to a lesser extent due to the surface asperities that prevent close contact with other particles. It is also proven that having greater projected areas brings lesser particle velocity and therefore better particle deposition in the targeted area [23]. Spray-dried particles usually introduce densities lower than 0.5 g/mL, sometimes densities even lower than 0.1 g/mL are presented. This in turn leads to smaller aerodynamic diameters and better particle deposition [20].

- **Particle size**

Particle size is considered to be a linear length quantity measured in meters [24]. For spheres, this number is defined as the geometric diameter or the radius, while for non-spherical particles it is determined by measuring a size-correlated property i.e. derived diameters [24]. One of the most used derived diameters is the equivalent diameter that is divided into several different diameters such as volume equivalent sphere diameter $D_{Volume}$, surface equivalent sphere diameter $D_{Surface}$, Stoke's diameter $D_S$ and hydrodynamic equivalent diameter $D_H$ etc. [24]. For inhalable particles the most relevant diameter is the aerodynamic equivalent diameter $D_{ae}$. The aerodynamic equivalent diameter of a particle is the diameter of a unit density sphere (spherical drop of water) with the same settling velocity as the particle. The aerodynamic equivalent diameter helps to describe the behavior of the particle in air besides providing an indication on the site of deposition in lung.

For good penetration into the pulmonary airways, it is often required that the particles have an aerodynamic particle size between 1-5 µm [4][23]. Particles with aerodynamic diameters larger than 5 µm typically deposit in the oral cavity and the upper respiratory tracts. Contrarily, particles with aerodynamic diameters smaller than 0.5 µm have a tendency of not depositing at all and falling out with the exhaled air [25].
The aerodynamic diameter, $D_{ae}$, is defined by the following equation, **Equ.2**, where $D_{eq}$ = diameter of equivalent volume sphere, $\rho$ = particle bulk density, $\rho_0$ = unit density (water mass density = 1 g/cm$^3$) and $x$ is the dynamic shape factor ($x$ = 1 for spherical particles) [25].

$$D_{ae} = D_{eq} \sqrt{\left(\frac{\rho}{\rho_0 \cdot x}\right)} \quad \text{Equ.2}$$

To influence the aerodynamic diameter of a particle, one of the three existing parameters in the expression must be changed [23][25]. Decreasing particle size, decreasing particle density or increasing the dynamic shape factor can lead to decreasing the aerodynamic diameter [25].

- **Particle size distribution**

The particle size distribution affects the deposition of drug particles in the lungs. Various methods are available for determining particle size distribution. These techniques include inertial methods such as cascade impactor, light scattering methods such as Dynamic Light Scattering (DLS) and laser diffraction analysis, imaging methods like photoanalysis and optical counting methods [25]. However, the aerodynamic particle size distribution should be narrow within a size range favorable for inhalation, between 1 µm and 5 µm [26]. In this project, the geometric standard deviation GSD is obtained from the NGI measurements and refers to the width of the particle size distribution. Small GSD numbers mean narrow particle size distributions while high GSD numbers indicate wide particle size distributions.

- **Particle shape**

Pharmaceutical powder particles are often non-spherical and irregularly shaped. It has been pointed out in vitro studies that elongated, porous, crumpled and needle- or pollen-shaped particles have superior deposition properties in the lungs [1]. This is because of the reduced tendency for agglomeration because of the minimal particle interactions [1]. In an article that has been referred to in this work, it is claimed that spherical particles are favorable for the better flowability properties because of the fact that irregular and uneven surfaces lead to extra interactions between the particles causing poor powder flowability [27]. Compared to other cocrystallization methods, spray drying is superior in generating spherical particles in the inhalable range (1-5 µm) with narrow particle size distribution [25][27]. It is also mentioned that completely spherical particles have great potential to reach the alveolar regions although they are difficult to produce by spray drying. Size and shape of the particles can be analyzed using Scanning Electron Microscopy (SEM), an analytical tool that provides
2-dimensional images of the analyzed solids revealing information about the sample morphology and microstructure.

- **Flowability**

Powder flowability is the ability of powder to flow through equipment under specified conditions. To study powder flowability several factors must be taken into account. Determining the relation between bulk densities and tapped densities, estimating angle of repose, powder flow rate and shear testing is highly recommended. Hausner ratio and Carr's index, **Equ.3 and Equ.4** respectively, indicate the flow properties of powders. If Hausner ratio is less than 1.25, the powder is free flowing and a Hausner ratio higher than 1.25 indicates poor flow properties. Interpreting Carr's index, a numerical value of 5-15 suggests excellent flowability, whereas a value between 12 and 16 indicates good flowability and a value between 18-21 fair flowability. Values higher than 23 verify poor flowability. However, any value less than 21 is good enough to obtain good powder flowability.

\[
\text{Hausner ratio: } HR = \frac{\rho_{\text{tap}}}{\rho_{\text{bulk}}} \quad \text{Equ.3}
\]

\[
\text{Carr's index: } CI = \left(\frac{\rho_{\text{tap}} - \rho_{\text{bulk}}}{\rho_{\text{tap}}}\right) \times 100 \quad \text{Equ.4}
\]

Powder flow properties can be improved by optimizing particle size, particle shape, particle surface properties and water content by the addition of magnesium stearate and colloidal silicon dioxide.

**1.4.4 In vitro aerosolization behavior**

The inhalation behavior and drug deposition can be tested using an inhaler device such as next generation pharmaceutical impactor NGI, **Figure 7**. The NGI device contains eight stages; five of these stages are in the range of inhalation (0.5-5 µm). The airflow passes through the device in a series of nozzles causing particle sizing. The samples from each stage are dissolved in an appropriate solvent and collected for analysis. Mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle fraction (FPF) are used to describe powder dispersion properties in the NGI [6][11]. MMAD, mass median aerodynamic diameter, can be seen as the average particle size and GSD, geometric standard deviation, is viewed as the spread of the particle size distribution. Small GSD numbers refer to narrow particle size distributions while high GSD numbers indicate wide particle size distributions. FPF is obtained by dividing fine particle dose FPD by the total delivered dose and represents the fraction of drug that deposits in the airways and exerts a pharmaceutical effect.
15

Figure 7: Next generation impactor NGI.

1.5 Theophylline

Theophylline (THF), Figure 8, is a widely studied bronchodilator and central nervous system stimulant, used for treating several respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), anesthesia, cystic fibrosis and infectious pulmonary diseases [6][28][29]. Just like other bronchodilators, THF targets special receptors throughout the lungs. The best bronchodilating effect is obtained when reaching receptors in the smooth muscle within the conducting airways [30]. THF is reported to exist as four different polymorphs (I, II, III and IV) and as a hydrate stable in water [6][29].

Figure 8: Chemical structure of theophylline.

Theophylline has previously been used orally, but oral delivery of this drug has been gradually reduced over the years due to the arrival of more selective inhalable substances with fewer side effects such as beta-2 agonists and corticosteroids [31]. In the past, theophylline was the most prescribed medication for COPD, but it lost popularity because of its side effects. However, it is possible that theophylline has many advantages other than bronchodilatation and that needs to be investigated.

Various mechanisms of action are available for explaining the behavior of theophylline in the human body but the main mechanism of action for theophylline is not completely clarified or understood yet [31]. However it is known that theophylline restrains the inflammatory reaction caused by asthma and other diseases [31].
Theophylline has both hydrogen bond donors and hydrogen bond acceptors. These characteristics make theophylline an appropriate candidate for cocrystal formation. In fact, theophylline cocrystals have successfully been prepared and reported by researchers and scientists in several significant studies. Although the majority of theophylline cocrystals have been made by traditional cocrystallization methods, spray dried theophylline cocrystals have also been prepared by scientists. Theophylline-saccharin cocrystals have been made previously by spray drying [6][25]. However, spray dried theophylline-citric acid cocrystals and theophylline-flufenamic acid cocrystals have not been reported earlier. The cocrystal formers included in this work are citric acid, flufenamic acid and saccharin. They are listed below in Figure 9.

![Chemical structures of theophylline co-formers.](image)

Figure 9: Chemical structures of theophylline co-formers.

Citric acid (CA) is a natural carboxylic acid present in the cells of different living organisms such as human, plant and animal. Due to the non-toxic profile of citric acid, it is widely used in the food industry, pharmaceutical industry and also in metallurgical applications [32]. As to flufenamic acid (FFA), it is a non steroidal anti-inflammatory drug (NSAID) used for pain relief due to its analgesic, anti-inflammatory and antipyretic properties [29]. Saccharin is a widely used artificial sweetener in food and pharmaceutical industries. Basic physicochemical properties of the given starting materials are presented in the table below, Table 1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS-nr</th>
<th>$M_w$</th>
<th>$pK_a$</th>
<th>Density</th>
<th>$T_m$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline anhydrous</td>
<td>58-55-9</td>
<td>180.16</td>
<td>8.6±0.5</td>
<td>1.465±0.06</td>
<td>273</td>
</tr>
<tr>
<td>Citric acid monohydrate</td>
<td>5949-29-1</td>
<td>210.14</td>
<td>3.13, 4.76, 6.4</td>
<td>1.5</td>
<td>154</td>
</tr>
<tr>
<td>Flufenamic acid</td>
<td>530-789</td>
<td>281.23</td>
<td>3.67±0.36</td>
<td>1.395±0.06</td>
<td>135</td>
</tr>
<tr>
<td>Saccharin</td>
<td>81-07-2</td>
<td>183.18</td>
<td>1.6±0.1</td>
<td>0.828</td>
<td>229</td>
</tr>
</tbody>
</table>
2. Aims

2.1 General aims

General aims of the project were to explore the potential of novel approach, which combines crystal and particle engineering in a single step. And also improve the spray dried co-crystal properties, to investigate the possibility for minimizing the use of coating agents or lactose.

2.2 Specific aims

Specific aims were to produce inhalable theophylline cocrystals by spray drying, determine solid state properties, particle size/shape and flowability and study in vitro aerosolization behavior for the drug alone and the drug mixed with lactose.
3. Materials and methods

3.1 Chemicals

Theophylline anhydrous (CAS# 58-55-9), citric acid monohydrate (CAS# 5949-29-1), flufenamic acid (CAS# 530-789) and saccharin (CAS# 81-07-2) were obtained from Fisher Scientific (Loughborough, UK), Scharlau (Barcelona, Spain), Fluka (Germany) and Sigma-Aldrich (Steinheim, Germany) respectively. Sodium dodecyl sulfate SDS was from Fluka and Pluronic® F68 Poloxamer surfactant was from BASF (Ludwigshafen, Germany). Anhydrous acetic acid glacial (100%) and ammonia solution (25%) were purchased from Merck KGaA (Darmstadt, Germany). Acetonitrile of HPLC gradient grade was from Fisher Scientific (Loughborough, UK). Lactose conditioned carrier (Art. No. 290005100, batch No. 1301) and lactose fines (Art. No. 297042000, batch No. 307701, D50=3 µm) were from AstraZeneca (Mölndal, Sweden).

3.2 Solvents

Ethanol (99.5%) of analytical grade was purchased from CCS Healthcare AB (Dalarna, Sweden). methanol was from Merck KGaA (Darmstadt, Germany). Acetone of analytical reagent grade was from Fisher Scientific (Loughborough, UK) and ethyl acetate was from Sigma-Aldrich (Steinheim, Germany).

3.3 Design of experiments

Different process parameters have different impact on the quality of the spray dried product. Statistical design of experiments DoE is a typical statistical way for method optimization in the pharmaceutical industry. Significant factor changes with the most influence on the final product are considered to improve the effectiveness of the process with the least number of experimental runs [33][34]. A full factorial 2-level interaction model design was implemented using the software MODDE Version 10 by Umetrics AB to look into the most significant process parameters. The initial spray drying experiments did not give any clear results regarding yield and particle size, it was therefore advantageous to divide the experiments into separate groups with defined conditions. The first group would represent good drying and the second would stand for bad drying. Good drying experiments were carried out using high inlet temperatures and low feed rates, while bad drying experiments had lower inlet temperatures and higher feed rates. The selected factors for the experimental design were inlet temperature at the levels 80°C and 120°C and feed rate at the levels 10 mL/min and 20 mL/min.
The responses used in the optimization matrix were process yield and particle size distribution. The total number of experiments in this section was 8 experiments and the chosen cocrystal system was THF-FFA. The software MODDE was used to generate response predictions for experimental work, the generated design matrix and the graphs are listed under results.

3.4 Experimental section

3.4.1 Determination of solid state properties

Firstly, the starting materials were analyzed by PXRD, TGA and DSC. Particle size distribution, tapped density and bulk density were also measured to estimate flowability of the raw starting materials.

DSC analysis was performed using a Q-2000 differential scanning calorimeter from TA Instrument (New Castle, USA). The analysis was performed using standard mode, custom test with T-Zero aluminum pans and lids and a flow rate of 10 °C/min. Sample weight was 3-6 mg and final temperature for THF-FFA and THF-SAC was set to 220 °C and 230 °C respectively. TGA data were collected using a Q-500 from TA Instruments (New Castle, USA). The pans used were platinum pans, sample weight was 3-6 mg and the heat flow rate was set to 10 °C/min. The data from DSC and TGA were analyzed using the software Universal Analysis 2000. Powder X-ray diffraction patterns were generated using a Bruker AXS diffractometer (Karlsruhe, Germany) and analyzed using the software X’ Pert Data Viewer.

Particle size distribution measurements were carried out by laser diffraction using Sympatec RODOS with HELOS as the laser diffraction sensor from Sympatec GmbH (Clausthal-Zellerfeld, Germany). The dispersion pressure was set to 4 bar in all experiments. The GeoPyc 1360 T.A.P Density Analyzer from Micromeritics (Norcross, USA) was used for the tap density measurements. The weights used were between 1 and 3.5 g, the number of preparation cycles was set to 5, the measured cycles to 3 and the pressure applied was 10 Newton in all of the measurements. Bulk density was measured using bulk density apparatus (cylinder volume 1.60 mL).

Cocrystal particle images were produced using a scanning electron microscope Quanta 200 SEM from FEI Company (Eindhoven, The Netherlands). The images were generated at high vacuum mode. Prior to screening, samples were coated with gold using a sputter coater in argon atmosphere at 20 mA for 250 seconds.
3.4.2 Solubility measurements

Solubility measurements were performed to determine the solubility of the given compounds and understand their behavior in the selected solvents and co-solvent systems. Five solvents of interest were chosen to find the most suitable solvent for spray drying. The solvents chosen were water, methanol, ethanol, ethyl acetate and acetone. Solubility at RT was measured using gravimetric analysis by placing raw starting materials in vials containing the given solvents to gain supersaturated solutions. The mixtures were left for agitation for ca 48 hours to achieve equilibrium. Subsequently, a small amount of solution from each system was transferred with injection filter into two new clean tubes. The mass of the solution was determined prior to evaporation. After complete evaporation, the remaining solids were weighed and the mean value for the solids was calculated. Solubility at 50°C was estimated using Crystal16® multiple reactor system. The method was based on turbidity analysis where the temperature interval was set to 15-55 ºC, the stirring speed was set to 850 rpm and the duration of the analysis was approximately 4 days. Solubility values from the gravimetric analysis and turbidity were plotted against temperature.

3.4.3 Preparation of theophylline cocrystals by slurry conversion

Theophylline cocrystals THF-CA, THF-FFA and THF-SAC were made by slurry crystallization. In 25 mL E-flasks containing 5 mL coformer saturated ethanol 0.51 g THF and 0.58 g CA, 0.50 g THF and 0.51 g SAC, 0.49 g THF and 0.76 g FFA were each added. The flasks were stirred for ca 20 hours and THF-CA cocrystals were filtered by vacuum and collected. THF-FFA and THF-SAC co-crystals were slurried for 3 additional days before collection and filtration. All of the three products were put into a vacuum oven overnight to get rid of the residual solvent. The products were stored at room temperature and relative humidity of 20% before further analysis.

3.4.4 Preparation of spray dried raw materials

The spray drying experiments were carried out using a Buchi B-290 mini spray dryer from Buchi Labortechnik AG (Flawil, Switzerland) supplied with a peristaltic pump, standard atomizer, and a high performance cyclone. Nitrogen gas was used as the drying gas. Solutions of the raw starting materials in EtOH were prepared and spray dried under controlled conditions. The process parameters used are listed in Table 2. The solid concentration of the spray dried solutions was 3% w/w for the co-formers and 0.4% w/w for theophylline due to the limited solubility of theophylline.
Table 2: Processing parameters for the spray drying of raw materials.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Substance</th>
<th>Solvent</th>
<th>Solid conc. (%)</th>
<th>Inlet temp (°C)</th>
<th>Feed rate (mL/min)</th>
<th>Air flow rate (L/h)</th>
<th>Aspiration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>EtOH</td>
<td>0.4</td>
<td>100</td>
<td>10</td>
<td>445</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>CA</td>
<td>EtOH</td>
<td>3</td>
<td>100</td>
<td>10</td>
<td>445</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>FFA</td>
<td>EtOH</td>
<td>3</td>
<td>100</td>
<td>10</td>
<td>445</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>SAC</td>
<td>EtOH</td>
<td>3</td>
<td>100</td>
<td>10</td>
<td>445</td>
<td>100</td>
</tr>
</tbody>
</table>

3.4.5 Preparation of theophylline cocrystals by spray drying

The preliminary spray drying of cocrystals started with spray drying of THF-SAC, THF-FFA and THF-CA systems from ethanol. These experiments were performed to identify the process conditions that could yield good cocrystals. The initial process yields were not good enough, optimization was therefore necessary. The maximum solid concentration could only reach 0.8-0.9% (w/w) for both cocrystal components, therefore solubility improvement by using cosolvent systems was applied. The tested cosolvent systems were 95% ethanol-5% water, 90% ethanol-10% water and 90% acetone-10% water. The solid concentration could be increased to 2-3% but the yields did not improve. Pure methanol, acetone and ethyl acetate were also tested.

To add more structure to the experiments, it was decided to run a few experiments using good drying conditions and other using bad drying conditions. The solutions were spray dried from pure ethanol to avoid complex co-solvent systems. The difference between the analyzed particles was considered to take forward work to the final step.

The final spray drying experiments for the cocrystal systems THF-FFA and THF-SAC were performed using the following parameters and conditions, Table 3. THF-CA system was not considered due to poor yields.

Table 3: Processing parameters for the final spray drying experiments.

<table>
<thead>
<tr>
<th>Cocrystal System</th>
<th>Solvent</th>
<th>Solid conc. (%)</th>
<th>Inlet temp (°C)</th>
<th>Outlet temp (°C)</th>
<th>Feed rate (mL/min)</th>
<th>Air flow rate (L/h)</th>
<th>Aspiration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF-FFA</td>
<td>EtOH</td>
<td>0.9</td>
<td>120</td>
<td>77</td>
<td>5.0</td>
<td>536</td>
<td>100</td>
</tr>
<tr>
<td>THF-SAC</td>
<td>EtOH</td>
<td>0.9</td>
<td>120</td>
<td>82</td>
<td>3.0</td>
<td>536</td>
<td>100</td>
</tr>
</tbody>
</table>
The last experiments were repeated with the same processing parameters under identical conditions using 2% sodium dodecyl sulfate (SDS) to see if the surfactant could solve the adhesion problem, but the yields remained alike. Also another surfactant (Pluronic® F68 Poloxamer) was tested but in vain. Time constraints did not allow testing of different concentrations of these two surfactants.

3.4.6 Preparation of carrier based drug

The ordered mixtures consisted of 2% API, 8% lactose fines and 90% lactose carrier particles. The total mass of the ordered mixtures was 10 g. The components were added, according to the sandwich method, to a test tube containing three Syalon ceramic beads. The mixture was shaken manually by hand for 5 minutes and transferred to a new clean jar. The batches made included ordered mixture of THF-FFA, THF-SAC and spray dried theophylline, Table 4.

**Table 4:** Material amounts used in preparing ordered mixtures.

<table>
<thead>
<tr>
<th></th>
<th>API (mg)</th>
<th>Lactose fine (mg)</th>
<th>Lactose carrier (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF-FFA</td>
<td>205</td>
<td>803</td>
<td>9077</td>
</tr>
<tr>
<td>THF-SAC</td>
<td>204</td>
<td>803</td>
<td>9011</td>
</tr>
<tr>
<td>THF</td>
<td>203</td>
<td>801</td>
<td>8998</td>
</tr>
</tbody>
</table>

3.4.7 Next generation impactor experiments

In vitro aerosolization behavior was evaluated using Next Generation Impactor (NGI-0057) from MSP Corporation (Shoreview, MN, USA). Doses were approximately 10 mg of powder per dose. Flow rate was set to 65 L/min and inhalation time was 3.7 seconds. Three doses were taken in every measurement with two replicates for every sample. The inhaler used was a screenhaler with a Turbuhaler® mouthpiece from AstraZeneca. The instrumentation included next generation impactor (NGI), induction port, set of cups in tray, a flow rate meter for the flow rate settings, device for measuring back pressure and shaking stations for the cup trays and the induction port. Glycerol was smeared on the cups to prevent the powder from bouncing further. After the runs, the powder in the cups was dissolved in 15 mL buffer solution and samples were collected after 15 minutes of shaking for the UPLC analysis.

3.4.8 Ultra performance liquid chromatography UPLC

Ultra Performance Liquid Chromatography (UPLC) from Waters (Milford, USA) was used for the determination of the drug concentrations. A freshly made acetate buffer solution (pH 4.3) was used in
the chromatographic experiments. The buffer solution was made of ammonia and acetic acid and diluted to 50 mM with milli-Q water. Acetonitrile (10%) was added to the buffer to accelerate the elution of the compound. The column used was a Waters Acquity UPLC BEH C18 column (2.1 mm X 100 mm). The flow rate was set to 0.3 mL/min, and the injection volume to 0.5 µL. The run time was 5 minutes and elution time 1.8 minutes. The detector used was a TUV detector set to measure at 270 nm. All of the runs were based on isocratic elution. A standard curve was initially constructed using stock solutions with exact concentrations of theophylline dissolved in buffer. The concentrations used were 0.01, 0.05, 0.1, 0.15, 0.2 and 0.4 mg/mL.
4. Results and discussion

4.1 Raw materials

4.1.1 Basic solid state properties

XRD data showed the crystal patterns of the raw materials, Figure 10. The measured melting point for theophylline is 271 °C which concurs with the reported melting point in literature, Figure 11 [35]. The measured melting point of citric acid anhydrate is 153 °C which agrees with the results from the literature, Figure 11 [36]. The measured melting point of flufenamic acid is 133 °C and it agrees with the melting point reported in literature, Figure 11 [37]. The melting point of saccharin from DSC measurements and from literature was found to be 229 °C, Figure 11 [38].

Figure 10: PXRD graphs for raw THF, CA, FFA and SAC (intensity as a function of 2-theta angle).
4.1.2 Bulk properties

In addition to basic solid state analysis, particle size distribution, Figure 12, tap density and bulk density were measured. Carr’s index and Hausner ratio were calculated using tap density and bulk density, all of the determined values are listed in the table below, Table 5.

Figure 11: DSC thermograms (heat flow(W/g) vs. T(ºC)) for THF, CA, FFA and SAC.

Figure 12: Particle size distributions for the raw starting materials (density distribution q^4 versus particle size µm)
Table 5: Measured and calculated quantities for the raw materials.

<table>
<thead>
<tr>
<th>Compound</th>
<th>VMD(^1) (µm) (n=3)</th>
<th>Bulk density (g/cm(^3)) (n=3)</th>
<th>Tap density (g/cm(^3)) (n=3)</th>
<th>Carr index</th>
<th>Hausner ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>5.42±0.24</td>
<td>0.26±0.01</td>
<td>0.54±0.001</td>
<td>51.27</td>
<td>2.05</td>
</tr>
<tr>
<td>CA</td>
<td>316.60±44.19</td>
<td>0.84±0.002</td>
<td>0.99±0.005</td>
<td>14.96</td>
<td>1.18</td>
</tr>
<tr>
<td>FFA</td>
<td>153.20±8.61</td>
<td>0.80±0.04</td>
<td>0.91±0.004</td>
<td>11.96</td>
<td>1.14</td>
</tr>
<tr>
<td>SAC</td>
<td>10.40±0.29</td>
<td>0.32±0.02</td>
<td>0.69±0.002</td>
<td>54.18</td>
<td>2.18</td>
</tr>
</tbody>
</table>

As seen above, flowability improves with higher particle size; citric acid and flufenamic acid have the highest particle sizes, thus the best values for Carr index and Hausner ratio.

4.2 Solubility of the different materials in selected solvents

Solubility at room temperature was measured using gravimetric analysis, while solubility at 50°C was estimated using turbidity analysis by Crystal16\(^\circledR\) multiple reactor system. The solubility values were plotted against temperature, Figure 13. It is apparent from the graph that theophylline solubility profile differs dramatically from the solubility profiles of its co-formers. Due to the huge difference in solubility in the solvent studied, all of the theophylline cocrystal systems included in this work, are incongruent. Some of the bars in the graphs below are not visible due to scaling factors.

![Figure 13: Solubility profiles of THF, CA, FFA and SAC at 25 °C (1) and 50 °C (2).](image)

\(^1\) VMD=Volume Mean Diameter
4.2.1 Raw materials in solvents

THF exists in four anhydrous polymorphic forms (I, II, III and IV) and a monohydrate that is formed when anhydrous theophylline comes in contact with water [6]. The most stable form at room temperature is the anhydrous form II. Theophylline form III is considered to be a metastable form and converts to form II easily. When heating, form IV converts to form II, further heating leads to the conversion of form II to form I. Both forms I and II transform to form IV through solvent mediated conversion [39]. XRD graphs verified the existence of two different forms of theophylline, Figure 14.

Facts on CA reveal that anhydrous citric acid has two forms, and it also exists as a monohydrate. XRD measurements showed four different forms of CA, Figure 10 & Figure 15.

FFA is known to have many different polymorphs, at least nine polymorphs I-IX [37]. XRD data from this work showed three different forms of FFA, Figure 10 & Figure 16.

SAC is a non-hygroscopic acidic compound which is not soluble in water at room temperature. Different polymorphs of saccharin have not yet been reported and XRD graphs of saccharin showed similar patterns in all of the solvents, Figure 10.

**Figure 14** (intensity as a function of 2-theta angle): Theophylline monohydrate in water and theophylline anhydrous in MeOH, EtOH, EtOAc and acetone.
4.3 Cocrystals made by slurry conversion

The yields of the generated cocrystals were 64% for THF-CA, 86% yield for THF-SAC and 80% for THF-FFA. TGA and DSC analysis on the traditional co-crystals showed that co-crystal formation was successfully achieved, Figures 17-20. The melting points of the co-crystals are between the melting point of THF and the melting point of the co-former for the cocrystal systems THF-CA and THF-FFA. For the THF-SAC system, the cocrystal has a lower melting point than its two components. TGA-graphs show that there is no residual solvent remaining in the crystal structures and the decomposition of the material begins after the melting point, Figure 17. XRPD graphs show new crystal patterns that
differ from the starting materials which is also an indication for successful cocrystal formation, Figure 21.

Figure 17: DSC (heat flow(W/g) vs. T(°C)) overlaid by TGA (weight(%) vs. T(°C)) for THF-CA (left), THF-FFA (middle) and THF-SAC (right).

Figure 18: Traditional THF-CA co-crystals compared to the starting material; THF and CA.
**Figure 19:** Traditional THF-FFA co-crystals compared to the starting material; THF and FFA.

**Figure 20:** Traditional THF-SAC co-crystals compared to the starting material; THF and SAC.
The particle size distributions for the generated co-crystals were measured using laser diffraction; Sympatec, dry disperser RODOS, Figure 22. Densities and flowability properties are presented in Table 6.

### Table 6: Properties of the traditionally made theophylline cocrystals.

<table>
<thead>
<tr>
<th>Compound</th>
<th>VMD (µm)</th>
<th>Bulk density (g/cm³)</th>
<th>Tap density (g/cm³)</th>
<th>Carr index</th>
<th>Hausner ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF-CA</td>
<td>4.160±0.014</td>
<td>0.439±0.002</td>
<td>0.667±0.003</td>
<td>34.3</td>
<td>1.52</td>
</tr>
<tr>
<td>THF-FFA</td>
<td>6.275±0.106</td>
<td>0.305±0.025</td>
<td>0.627±0.003</td>
<td>51.3</td>
<td>2.05</td>
</tr>
<tr>
<td>THF-SAC</td>
<td>5.265±0.021</td>
<td>0.322±0.012</td>
<td>0.510±0.003</td>
<td>36.8</td>
<td>1.58</td>
</tr>
</tbody>
</table>
4.4 Spray dried raw materials

All of the spray dried raw materials were crystalline at room temperature and a relative humidity of ca 20%. Modulated DSC did not show any T_g for the analyzed substances and XRD peaks remained crystalline. As mentioned before, theophylline, citric acid and flufenamic acid can convert into different forms depending on the relative humidity (RH). It was found that theophylline anhydrate transforms into theophylline monohydrate at 75% RH [34]. As to citric acid, the conversion from the anhydrous form to the monohydrate requires a minimum of 73% RH [40]. For flufenamic acid, the minimum relative humidity for hydration was not found in literature. However, forms I and III of flufenamic acid are physically stable under the conditions of 40 °C and 96% RH for 2 months [41].

Solid state analysis confirmed the same melting points for spray dried materials to that of untreated raw materials. Theophylline, flufenamic acid and saccharin had the same crystalline peaks as the raw materials while citric acid had the form from when it was slurried in ethanol. Median particle size measurements gave the results presented in Figure 23. Tap density, bulk density and flow properties are included in Table 7.

![Particle size distributions for the starting materials spray dried.](image)

**Figure 23:** Particle size distributions for the starting materials spray dried.

**Table 7:** Measured and calculated quantities for the spray-dried raw materials.

<table>
<thead>
<tr>
<th>Compound</th>
<th>VMD (µm) n=2</th>
<th>Bulk density (g/cm³) n=3</th>
<th>Tap density (g/cm³) n=3</th>
<th>Carr index</th>
<th>Hausner ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>2.47±0.21</td>
<td>0.16±0.06</td>
<td>0.423±0.004</td>
<td>61.9</td>
<td>2.6</td>
</tr>
<tr>
<td>CA</td>
<td>6.37±1.31</td>
<td>0.17±0.01</td>
<td>0.648±0.013</td>
<td>73.2</td>
<td>3.7</td>
</tr>
<tr>
<td>FFA</td>
<td>5.13±0.47</td>
<td>0.27±0.01</td>
<td>0.536±0.002</td>
<td>48.6</td>
<td>1.9</td>
</tr>
<tr>
<td>SAC</td>
<td>2.15±0.78</td>
<td>0.32±0.04</td>
<td>0.50±0.02</td>
<td>35.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>
The obtained process yields for spray dried theophylline, flufenamic acid, saccharin and citric acid were 25%, 60%, 65% and 10% respectively.

4.5 Coocrystals made by spray drying

The initial cocrystal spray drying experiments were planned using DoE but the yields were very poor (ca 3% for THF-CA, 10% for THF-FFA and THF-SAC). Small amounts of particles could have passed through the filter but the main fraction of the material remained on the walls of the high performance cyclone. The spray drying process parameters were varied to see if there would be any improvement in the process yields. The parameters changed were inlet temperature, feed rate, atomization and total solid concentration through using cosolvent systems. The problem of poor yields could not be eliminated by varying the process parameters; therefore another type of cyclone was tested (standard cyclone). Standard cyclone showed that sticking to the walls of the cyclone was reduced but particle size was not in the inhalation range. It was therefore necessary to go back to high efficiency cyclone to acquire suitable particle size distributions for the spray dried cocrystals.

The main loss of yield was due to sticking to the cyclone walls. Sticking on the cyclone walls could be explained with a few different hypotheses. Stickiness can for example be related to the glass transition temperature. It is experimentally known that amorphous materials with low T_g have a tendency to stick on surfaces. Glass transition temperature for the spray dried materials could not be determined but on the other hand, the high melting points of the cocrystals suggest that the glass transition temperatures are relatively high. Also, the outlet temperature in the spray drying experiments was kept below the temperature interval that was considered to be close to T_g.

The other hypothesis that was discussed during this project was particle agglomeration on the cyclone wall. Usually, high efficiency cyclones allow more particle agglomeration than other normal cyclones because they separate smaller particles. Small particles tend to agglomerate; the smaller the particles, the higher the tendency for agglomeration. It is known from literature that agglomeration in cyclone is higher for the high performance cyclones [42]. Surface active compounds can sometimes be added to the solution of small particles to prevent particle growth. During optimizing the experiments, particle size measurements were done on particles from the collection jar and particles from the cyclone at the same time. In the final experiments, particle size in the collection jar and in the cyclone was similar. Despite, the sticking problem was still present suggesting other mechanisms than aggregation playing a role in the sticking problem.

The latter spray drying experiments were performed under specific conditions (designed to be bad drying conditions and good drying conditions). That was done to better understand the mechanisms
behind particle formation. It was also determined to focus on one single cocrystal system (THF-FFA). The experimental overview is presented in the table below, Table 8:

**Table 8**: Process parameters and results for the good drying and bad drying experiments.

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Conc.%</th>
<th>Solvent</th>
<th>V (mL)</th>
<th>Tin (°C)</th>
<th>Feed (mL/min)</th>
<th>Atomization air (L/h)</th>
<th>Asp. %</th>
<th>Tout °C</th>
<th>Yield% (jar)</th>
<th>D50 (µm) jar</th>
<th>D50 (µm) cyc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9</td>
<td>EtOH</td>
<td>230</td>
<td>80</td>
<td>10</td>
<td>536</td>
<td>100</td>
<td>48</td>
<td>22</td>
<td>1.5</td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>EtOH</td>
<td>230</td>
<td>120</td>
<td>10</td>
<td>536</td>
<td>100</td>
<td>70</td>
<td>35</td>
<td>2.6</td>
<td>3.1</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>EtOH</td>
<td>230</td>
<td>120</td>
<td>20</td>
<td>536</td>
<td>100</td>
<td>57</td>
<td>6</td>
<td>2.0</td>
<td>6.4</td>
</tr>
<tr>
<td>4</td>
<td>0.9</td>
<td>EtOH</td>
<td>230</td>
<td>80</td>
<td>20</td>
<td>536</td>
<td>100</td>
<td>34</td>
<td>6</td>
<td>2.4</td>
<td>9.8</td>
</tr>
<tr>
<td>5</td>
<td>0.9</td>
<td>EtOH</td>
<td>230</td>
<td>80</td>
<td>20</td>
<td>536</td>
<td>80</td>
<td>30</td>
<td>4</td>
<td>6.9</td>
<td>12.6</td>
</tr>
</tbody>
</table>

In spray drying, higher concentrations lead to higher yields. This is mainly because of the fact that the amount of dissolved solid material in the droplets is higher with higher concentration. The purpose of using cosolvent systems in the initial optimizing experiments was primarily to increase the total solid concentration in the spray dried solution. Instead, the complexity of cosolvent systems made it difficult to locate conclusions. It was consequently preferred to go back to pure solvents when running the good drying and bad drying experiments.

The resulted powders (from collection jar and from the cyclone) were collected and analyzed by XRD, Figure 24, DSC, Figure 25 and TGA, Figure 26.

**Figure 24**: PXRD patterns for cocrystals collected from collection jar and cyclone in experiments (1-5) from Table 8.
Figure 25: DSC showing the melting point for the spray dried cocrystals in the experiments.

Figure 26: TGA showing decomposition of the spray dried THF-FFA cocrystals.

Solid state analysis did not show any major difference between the particles from the different experiments. In fact, all the spray dried cocrystals were crystalline and had similar crystalline patterns. In addition to solid state analysis, particle size measurements were made. The results showed that experiment 2 which had the best drying conditions was the most optimal experiment as it had the
highest yield (35%) and its particle size distributions for the jar particles and the cyclone particles were similar, Figure 27. For the other experiments, particle size distributions from the collection jar and cyclone did not match.

![Particle size distribution (jar red, cyclone blue) for the best experiment (EXP2).](image)

**Figure 27:** Particle size distribution (jar red, cyclone blue) for the best experiment (EXP2).

The experimental design model that was chosen to represent the system was an interaction full 2-factorial model fitted with MLR. Results for the yields from the collection jar for the experiments showed that inlet temperature $T_{in}$ has a positive effect while feed rate $FR$ has a negative effect on the yield. In other words, increasing inlet temperature or reducing feed rate leads to higher yields, Figure 28. The interaction between $T_{in}$ and $FR$ showed a negative effect.

![Coefficients (normalized) - (MLR)](image)

**Figure 28:** Results from experimental design concerning process yields and particle size.

Design of experiments for particle size distributions showed that inlet temperature $T_{in}$ and feed rate have a positive effect on particle size i.e. higher inlet temperature lead to bigger particles and also
higher feed rate gives bigger particles. While the interaction between feed rate and $T_m$ has a negative effect on particle size.

The parameters from the best experiment were chosen as the final experiment parameters. Only feed rate was reduced to obtain better yields. The yields for the spray dried cocrystals were 44% for THF-FFA cocrystals and 36% for THF-SAC cocrystals. The solid state properties of these materials were similar those of produced earlier batches.

**Figure 29:** PXRD pattern (intensity as a function of 2-theta angle) for the final THF-FFA cocrystals.

**Figure 30:** PXRD pattern (intensity as a function of 2-theta angle) for the final THF-SAC cocrystals.

Both THF-FFA and THF-SAC were pure crystalline cocrystals with XRD peaks consistent with the peaks for the traditionally made cocrystals, **Figures 29 & 30**. The melting points corresponded with the melting points for the traditionally made cocrystals. TGA showed no trace of residual solvent in the formulations, **Figure 31**.
Particle size distribution, bulk density, tap density and flow properties were determined for the cocrystal systems, Table 9. The low densities are indicative of good aerodynamic diameters. Particle size distributions are in the middle of the inhalation range, Figure 32 & 33, but due to the low particle size, the flow properties are not optimal.

Table 9: Properties for the final spray dried cocrystals.

<table>
<thead>
<tr>
<th>Cocrystal</th>
<th>$T_{\text{max}}$ (°C)</th>
<th>$T_{\text{onset}}$ (°C)</th>
<th>$\Delta H$ (J/g)</th>
<th>Bulk density (g/cm$^3$)</th>
<th>Tap density (g/cm$^3$)</th>
<th>Carr index</th>
<th>Hausner ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF-FFA</td>
<td>187.57±0.29</td>
<td>186.23±1.11</td>
<td>98.69±3.34</td>
<td>0.161±0.004</td>
<td>0.492±0.002</td>
<td>67.4</td>
<td>3.1</td>
</tr>
<tr>
<td>THF-SAC</td>
<td>204.87±0.17</td>
<td>202.90±1.32</td>
<td>136.60±3.10</td>
<td>0.194±0.003</td>
<td>0.441±0.003</td>
<td>55.7</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Figure 31: DSC (heat flow (W/g) vs. T(°C)) in combination with TGA (weight (%) vs. T(°C)) for THF-FFA and THF-SAC.

Figure 32: Particle size distribution for THF-SAC system. D10= 0.83±0.078, D50=2.69±0.068 and D90=6.96±0.707 (n=3)
Figure 33: Particle size distribution for THF-FFA system. D10= 0.79±0.029, D50=3.04±0.107 and D90=6.06±0.142 (n=3).

Furthermore, the stoichiometry of theophylline and coformers in the cocrystals was measured by NMR (400 mhz). From $^1$H NMR spectra, hydrogen atoms belonging to theophylline were assigned and integrated, Figure 34 & 35. Integration of hydrogen atoms in the coformer showed the stoichiometry of the cocrystal, Table 10. There was no trace of residual solvent (ethanol), in any of the graphs either.

Table 10: Calculated stoichiometry for the final cocrystals.

<table>
<thead>
<tr>
<th>Cocrystals</th>
<th>Stoichiometry %</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF-FFA</td>
<td>100:97</td>
</tr>
<tr>
<td>THF-SAC</td>
<td>100:86</td>
</tr>
</tbody>
</table>

Figure 34: $^1$H NMR spectrum for THF-FFA cocrystals in DMSO.
Figure 35: $^1$H NMR spectrum for THF-SAC cocrystals in DMSO.

$^{13}$C satellites that usually form 0.55% were taken into account when calculating the stoichiometric ratio for theophylline and coformers.

4.6 Aerosolization performance

The standard curve obtained from theophylline stock solutions, Figure 36, was used to calculate the concentrations of theophylline from next generation pharmaceutical impactor runs. Values for MMAD, GSD and FPF were then calculated using the associated template.

Figure 36: Theophylline standard curve made of 6 different concentration points.
For the ordered mixtures of THF-FFA, THF-SAC and spray dried THF, the drug fraction that reaches the lower airways is 32%, 26% and 31% of the total dose respectively. Corresponding fraction for pure formulations THF-FFA, THF-SAC and THF is 7%, 4% and 6% respectively. However, total retention is reasonable for all systems, Table 11. Delivered dose, the amount of drug released from the inhaler and available for inhalation or total dose minus retention in inhaler, is excellent for all the systems.

Moreover, concentrations from the NGI plates were plotted against the different NGI stages, Figure 37 & Figure 38. Stage 1 in the graphs represents mouthpiece, stage 2 throat and stages 3, 4 and 5 upper airways. Stages 6, 7, 8, 9 and 10 are viewed as lower airways. The last stage is the filter.

**Table 11:** Retention in inhaler, delivered dose and deposition for the formulations.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>THF-FFA ordered</th>
<th>THF-SAC ordered</th>
<th>THF ordered</th>
<th>THF-FFA</th>
<th>THF-SAC</th>
<th>THF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention in inhaler %</td>
<td>15.9</td>
<td>11.9</td>
<td>13.7</td>
<td>6.6</td>
<td>11.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Delivered dose %</td>
<td>84</td>
<td>88</td>
<td>86</td>
<td>94</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Deposition in mouth and throat %</td>
<td>32</td>
<td>35</td>
<td>29</td>
<td>24</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Lung deposited dose %</td>
<td>32</td>
<td>26</td>
<td>31</td>
<td>7</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

The used NGI template also provided information on fine particle fraction (FPF), mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD), Table 12.

**Table 12:** Information gained from the NGI template.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>THF-FFA ordered</th>
<th>THF-SAC ordered</th>
<th>THF ordered</th>
<th>THF-FFA</th>
<th>THF-SAC</th>
<th>THF</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPF %&lt;5 µm of DD</td>
<td>51.9</td>
<td>38.2</td>
<td>40.3</td>
<td>31.1</td>
<td>15.6</td>
<td>10.9</td>
</tr>
<tr>
<td>FPF %&lt;3 µm of DD</td>
<td>39.8</td>
<td>27.2</td>
<td>29.9</td>
<td>17.7</td>
<td>7.3</td>
<td>6.0</td>
</tr>
<tr>
<td>FPF %&lt;1 µm of DD</td>
<td>19.4</td>
<td>12.5</td>
<td>8.7</td>
<td>3.5</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>MMAD µm</td>
<td>1.88</td>
<td>2.33</td>
<td>2.23</td>
<td>3.19</td>
<td>4.10</td>
<td>3.69</td>
</tr>
<tr>
<td>GSD</td>
<td>3.82</td>
<td>2.46</td>
<td>2.04</td>
<td>1.92</td>
<td>1.95</td>
<td>2.02</td>
</tr>
</tbody>
</table>
FPF is usually associated with the homogeneity of the formulation, the higher the FPF, the better the homogeneity. As stated in the table, fine particle fraction is highest for the ordered THF-FFA formulation. Same system has the lowest aerodynamic diameter but the highest GSD. Theophylline by itself and ordered THF-SAC system have excellent aerodynamic diameters. Pure formulations have the lowest FPF and the highest MMAD, still within inhalation range. GSD for pure systems turned out to be the best. In general, inhalation behavior for the ordered cocrystal formulation THF-FFA is better than that for ordered theophylline. Ordered system of THF-SAC had an inhalation performance almost as good as for ordered theophylline. As to the pure cocrystals, they were better than pure theophylline.

Spray dried formulations are usually statically charged and “sticky” which can lead to agglomeration and lower inhalation performance. For more optimal results, flowability for the cocrystals should be improved. Using another type of inhaler may eliminate the problem of cohesive materials and may bring further insight into this issue. For the particles to be appropriate for inhalation, a fraction of 10-30% of the inhaled dose should pass through to the lower airways and this has been the case for the ordered formulations.
Figure 39: Screenhaler
5. Conclusions

Theophylline cocrystals were successfully produced by both traditional method and by spray drying. The spray dried cocrystals were primarily crystalline and the particle size was in the range of inhalation. The particle formation mechanism appears to be supersaturation and nucleation mediated. Flowability for the powders was not optimal but in vitro aerosolization behavior for the cocrystals showed a fair inhalation performance that was better than that for theophylline.

A large amount of the material was adhered to the cyclone walls. Neither varying the process parameters nor adding surfactants to the spray dried solutions could solve the sticking problem completely. Further work must be done to optimize the spray drying process and understand the mechanism behind sticking problem. Finding ways to improve flowability and reduce surface energy can prevent sticking in the cyclone and potentially improve inhalation performance. Aerosolization behavior can be investigated further using another type of inhaler and different types of formulations.
6. Future work

There are various techniques available for cocrystal formation. Spray drying provides the ability to control the process and obtain homogenous products. For theophylline cocrystals, the main problem was the sticking of the spray dried products to the walls of the cyclone. Therefore, other alternatives such as different cyclones and different apparatus should be investigated. Cocrystal particle formation by spray drying and inhalation behavior of wide range of pharmaceutical ingredients can be investigated. In addition to Screenhaler used in the study, other inhalers such as Turbuhaler® may be investigated. Finally, the performance of formulation of these cocrystals can also be investigated.
7. Acknowledgments

This project was performed at the department of pharmaceutical development at AstraZeneca R&D in Mölndal, Sweden. I would like to express my deep gratitude to my supervisors Sandra Gracin and Sitaram Velaga for the constructive comments, remarks and engagement through the learning process of this project. I would also like to thank all of the people who enthusiastically helped and shared their knowledge, experience and precious time.

Kuther Hadi
AstraZeneca R&D, Mölndal 2015
8. References


[39] Seton L, Khamar D, Bradshaw IJ, Hutcheon GA. Stability and conversion of theophylline solid forms.


Figure references from the internet:

http://www.fass.se/LIF/product?userType=2&npId=19961014000012

http://www.mspcorporation.com/products-detail.php/aerosol/m170-next-generation-impactor


9. Appendix

Table 1: Spray drying experiments of the starting materials.

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Substance</th>
<th>Solvent</th>
<th>Solid conc. %</th>
<th>Yield %</th>
<th>Tin (ºC)</th>
<th>Tout (ºC)</th>
<th>Feed rate (mL/min)</th>
<th>Atomization air (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>EtOH</td>
<td>0.3</td>
<td>27</td>
<td>100</td>
<td>64</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>SAC</td>
<td>EtOH</td>
<td>3.0</td>
<td>65</td>
<td>100</td>
<td>54</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>EtOH</td>
<td>0.4</td>
<td>20</td>
<td>100</td>
<td>63</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>CA</td>
<td>EtOH</td>
<td>3</td>
<td>7</td>
<td>100</td>
<td>63</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>FFA</td>
<td>EtOH</td>
<td>3</td>
<td>55</td>
<td>100</td>
<td>65</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>EtOH</td>
<td>0.4</td>
<td>16</td>
<td>110</td>
<td>69</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>CA</td>
<td>EtOH</td>
<td>5</td>
<td>2</td>
<td>100</td>
<td>63</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>EtOH</td>
<td>1.0</td>
<td>4</td>
<td>100</td>
<td>62</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>SAC</td>
<td>1.0</td>
<td>9</td>
<td>110</td>
<td>68</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>Acetone</td>
<td>0.3</td>
<td>6</td>
<td>100</td>
<td>67</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>CA</td>
<td>EtOH</td>
<td>3.1</td>
<td>9</td>
<td>120</td>
<td>75</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>12</td>
<td>CA</td>
<td>Acetone</td>
<td>3.2</td>
<td>11</td>
<td>100</td>
<td>65</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>CA</td>
<td>EtOH</td>
<td>10.3</td>
<td>3</td>
<td>120</td>
<td>73</td>
<td>10</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 2: The initial spray drying experiments of cocrystals to improve solubility and process yield.

<table>
<thead>
<tr>
<th>Exp. #</th>
<th>Cocrystal</th>
<th>Solvent</th>
<th>Total solid conc. %</th>
<th>Yield (%)</th>
<th>Tin (ºC)</th>
<th>Tout (ºC)</th>
<th>Feed rate (mL/min)</th>
<th>Atomization air (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF-SAC</td>
<td>EtOH</td>
<td>0.72</td>
<td>9</td>
<td>100</td>
<td>62</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>THF-SAC</td>
<td>EtOH</td>
<td>0.74</td>
<td>6</td>
<td>120</td>
<td>73</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>THF-SAC</td>
<td>EtOH</td>
<td>0.75</td>
<td>6</td>
<td>100</td>
<td>62</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>THF-SAC</td>
<td>EtOH</td>
<td>0.8</td>
<td>4</td>
<td>120</td>
<td>64</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>THF-SAC</td>
<td>EtOH</td>
<td>95% EtOH, 5% H2O</td>
<td>1.7</td>
<td>7</td>
<td>120</td>
<td>72</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>THF-SAC</td>
<td>EtOH</td>
<td>95% EtOH, 5% H2O</td>
<td>1.7</td>
<td>3</td>
<td>100</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>THF-SAC</td>
<td>EtOH</td>
<td>90% EtOH, 10% H2O</td>
<td>2.5</td>
<td>3</td>
<td>120</td>
<td>72</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>THF-SAC</td>
<td>EtOH</td>
<td>90% EtOH, 10% H2O</td>
<td>2.5</td>
<td>14</td>
<td>120</td>
<td>74</td>
<td>10</td>
</tr>
<tr>
<td>9*</td>
<td>THF-SAC</td>
<td>MeOH</td>
<td>90% EtOH, 10% H2O</td>
<td>2.5</td>
<td>17</td>
<td>120</td>
<td>78</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>THF-SAC</td>
<td>MeOH</td>
<td>90% Acetone, 10% H2O</td>
<td>2.1</td>
<td>-</td>
<td>120</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>THF-SAC</td>
<td>MeOH</td>
<td>90% Acetone, 10% H2O</td>
<td>3.0</td>
<td>3</td>
<td>120</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>THF-CA</td>
<td>EtOH</td>
<td>90% EtOH, 10% H2O</td>
<td>2.1</td>
<td>13</td>
<td>100</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
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*Experiment 9 was performed with another type of cyclone.
**Figure 1:** Theophylline peak in one of the UPLC runs.

**Figure 2:** A picture showing particle adhesion to the cyclone during a spray drying experiment.
Figure 3: Spray dried theophylline.

Figure 4: Spray dried THF-FFA cocrystals.

Figure 5: Spray dried THF-SAC cocrystals.