# Spray Drying Particles from Ethanol-Water Mixtures Intended for Inhalation

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Tiivistelmä/Referat – Abstract

Tämän työn tarkoituksena oli tutkia Büchin B-290 sumukuivaimen soveltumista inhalaatiopartikkelien valmistukseen ja sen prosessiparametrejen vaikutuksia tuotteen fysikokemiallisiin ominaisuuksiin. Lisäksi tutkittiin mahdollisuutta käyttää menetelmää partikkeleiden kiinteän tilan muuttamiseen amorfisesta kiteiseksi (engl. to anneal particles). Tavoite oli myös luoda tietoa liuottimen ja prosessiparametrien yhteisvaikutuksista lopputuotteen kiteisyyteen. Malliaineina käytettiin kahta lääkeainemolekyyliä : salbutamolisulfaattia ja budesonidia.

Sumukuivaus on 40-luvulta saakka ollut laajasti käytetty partikkelien tuotantomernetelmä. Prosessissa käsiteltävä, pumpattavissa oleva seos muokataan pisaroiksi. Pisarat kuivataan partikkeleiksi, jotka varastoidaan. Sumukuivausta käytetään mm. ruoka-aineiden, biomolekyylien ja lääkeaineiden käsittelyyn. Inhalaatiopartikkelien valmistuksessa se on kuitenkin suhteellisen uusi menetelmä. Tämä johtuu laatuvaatimuksista ja prosessin optimoinnin haasteista. Monista mahdollisista prosessiparametreista kolme laatuun ja kiinteään tilaan vaikuttavaa valittiin muuttujiksi tehtyihin kokeisiin: kiinteän aineen pitoisuus prosessoidussa liuoksessa, kuivatusilman lähtölämpötila ja orgaanisen liuottimen pitoisuus.

Alkeellista partikkelien kiinteän tilan muutosmenetelmää käytettiin partikkelien kiinteän tilan muutosherkkyyden tutkimiseen. Salbutamolisulfaatti altistettiin 65% suhteelliselle kosteudelle ja budesonidi 74% ja 100% etanoliaktiivisuuksille suljetussa astiassa. Partikkelikoko ja partikkelikokojakauma tutkittiin laserdiffraktiolla, kiteisyys jauheröntgenillä ja partikkelien ulkoasua arvioitiin elektronimikroskoopilla.

Sumukuivaaminen tuotti salbutamolisulfaatista amorfista ja budesonidista kiteistä materiaalia. Molemmat tuotteet olivat kokonsa puolesta (1-5µm) inhalaatiovalmisteiksi sopivia. Käytetyillä asetuksilla kiinteän tilan havaittiin riippuvan kohtalaisesti kiinteän aineen pitoisuudesta liuotinseoksessa. Sumukuivattu amorfinen salbutamolisulfaatti ja osittain amorfinen budesonidi saatiin onnistuneesti muuttumaan käsittelyllä kiteisempään tilaan. Lisätutkimuksia tarvitaan, jotta saadaan lisää tietoa sumukuivauksen käyttökelpoisuudesta inhalaatiopartikkelien tuotantoon. Kiinteän tilan muutoskinetiikka ja sen riippuvuus käytetystä menetelmästä ovat vielä suhteellisen tutkimattomia asioita.

Avainsanat – Nyckelord – Keywords
sumukuivaus, kiinteän tilan muutos, budesonidi, salbutamolisulfaatti, etanoli-vesi liuos

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Tiivistelmä/Referat – Abstract

The aim of this study was to obtain basic knowledge of the applicability of a Büchi Spray dryer B-290 for inhalation particle production and its process parameters effects on particle physicochemical properties. The possibility to anneal the particles where also studied. The greater goal was to provide some information about the solutes´ crystallization tendency related to chosen process parameters. Two active pharmaceutical ingredients, salbutamol sulphate and budesonide, where chosen as model substances.

Spray drying is a suspended particle processing system which is widely applied and it has been in use from the 1940s. The processed pumpable liquid which contains chosen substances is dispersed into droplets and dried to produce particles that are later collected. Spray dryer is used to process food, biochemical and pharmaceutical substances. In the field of inhalation particle processing, however, it is rather a new technology. This is because of the quality limitations of inhalable particles and the challenges in process optimization. From the many process parameters the concentration of the solid substances, inlet temperature and concentration of organic solvent were chosen as variables for the conducted experiments due to their apparent effects on product quality and especially on solid state.

A rudimentary box-annealing system was studied for spray dried substances to verify their solid state transformation tendencies. Salbutamol sulphate was annealed in a box with 65% relative humidity and budesonide in 74 % and 100% relative ethanol activities. Particle size and size distributions were measured with laser diffraction apparatus, crystallinity was analyzed with powder x-ray diffraction and particle morphology was studied with scanning electron microscope.

Salbutamol sulphate turned out to be amorphous and budesonide crystalline when spray dried. Both products were within the inhalable size range (1-5μm). Under the current setup the solid state quality of the products was found dependent on the concentration of the solid substances to some extent. Spray dried amorphous salbutamol sulphate was successfully anneaed to a crystalline material and partly crystalline budesonide was annealed to a more crystalline state. Further studies are needed to utilize the full potential spray drying has to offer for inhalation formulating. The kinetics of the annealing procedure and its dependency on the method used still remain largely unexplored.

Avainsanat – Nyckelord – Keywords
spray drying, annealing, budesonide, salbutamol sulphate, ethanol-water solutions

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# 1 INTRODUCTION

## 1.1 Background

Dry powder inhaler (DPI) is one of the main inhalation formulation alternatives to nebulizers and pressurized metered dose inhalers (pMDIs) for the delivery of the active pharmaceutical ingredients (API: s) into the human lungs (Newman *et al.* 2009). The basic composition of the DPI is the device with the packed powder formulation inside. In addition it may contain desiccants and possible inhalation aiding components such as compressed air. A DPI is considered as a quick and convenient device that is usually compact and portable. When compared with other formulation alternatives, it may be capable of delivering larger doses than pMDIs often with less variability in lung deposition and its aerosol is often formed solely due to an inhalation effort unlike in the other two types of devices. The DPI is considered to be a challenging device due to the interactions between the device, powder and patient (Bechtold-Peters *et al.* 2007).

The powder formulation used in the DPI device provides certain benefits when compared to the other two formulations (Bechtold-Peters *et al.* 2007). A powder formulation is considered as relatively stable, easy to handle and allows relatively flexible drug dose adjustment. The stability of the formulation and stability against microbiological contaminants are considered as superior when compared to the wet formulations. The device does not usually need to be cleaned or sterilized during the usage. A DPI dose ranges from micrograms to several tens of milligrams in short time frames (Newman *et al.* 2009). The DPI powder can consist of plain API (Healy *et al.* 2008; Sansone *et al.* 2009) or API with excipients up to over 99% of the formulation (Newman *et al.* 2009).

An optimal DPI formulation according to Chow *et al.* (2007) should have narrow aerodynamic particle size range, low surface energy and charge, non-spherical morphology, low density or high porosity as well as high physical and chemical stability. In addition to this it is considered as a rule that the particles are crystalline in nature to meet the stability requirements. To create a formulation with all these properties can be considered as challenging. The typical particle formation techniques include: micronization and blending, spray-drying, spray-freeze drying, emulsion based methods and supercritical antisolvents. For various reasons none of these fills the above requirements fully, but they have acted as a basis for many formulation strategies.

## 1.2 Spray drying

Spray drying is a rapid powder producing technique that disperses and dries liquid feeds to produce particles (Masters 2002). It typically produces solid or low density amorphous powders (Chow *et al.* 2007) but can produce particles with narrow aerodynamic particle size distribution (Cabral-Marques and Almeida 2009), porosity (Healy *et al.* 2008), non-spherical particles (Gad *et al.* 2012) and crystalline solid state (Bianco et al. 2012). The capability to produce particles with these claimed optimal properties Chow *et al.* (2007) combined with the simplicity and rapidity of the spray drying process makes it a promising technique for inhalation particle production.

The spray drying process itself has multiple variables (Buchi process parameters guide 2012) and the amount of variables increases even further when combined with the variables in the liquid feed (Masters 2002). This would theoretically allow the adjustment of the product quality quite efficiently. The challenges are the existence of significant interactions between different variables (Amaro *et al.* 2011; Gallo *et al.* 2011), the limited understanding on crystal growth, nucleation and supersaturated solutions (Vehring *et al.* 2007; Chen J. *et al.* 2011) and the slight apparent product specific dependency of the variables (Gallo *et al.* 2011).

The solid state quality of a spray-dried product is generally said to be amorphous due to the short time frames (Masters 2002). Despite this statement several variables, such as temperature (Mezzena *et al.* 2009) and solid concentration (Alves and Santana 2004; Bianco *et al.* 2012) are claimed to produce crystalline material in organic solvent alone (Alves and Santana 2004; Bianco *et al.* 2012) or from a mixture combined with water (Mezzena *et al.* 2009; Gad *et al.* 2011). Also other variables, such as feed rate (Islam and Langrish 2009), size of the nozzle orifice (Alves and Santana 2004), drying gas type (Islam and Langrish 2010b; Bianco *et al.* 2012), level of insulation (Islam and Langrish 2010a) and drying pressure (Eslamian and Ashgriz 2006) are claimed to affect the solid state of the product.

This study is focused in creating more understanding on the spray drying process by the temperature, solid concentration and organic solvent/water -ratio regulation. These variables were chosen due to their effects on crystallization and other important properties. Temperature has been found to affect for example particle size, yield and morphology (Maltesen *et al.* 2008; Cheow *et al.* 2010; Amaro *et al.* 2011) and density (Masters 2002). Solid concentration was found to effect density (Masters 2002) and humidity (Burnett *et al.* 2004) and organic solvent/water -ratio on particle size (Elversson and Millqvist-Fureby 2005a; Bürki *et al.* 2011) and particle shape (Gad *et al.* 2011; Kaialy *et al.* 2010).

## 2 BIOLOGICAL LIMITATIONS

The respiratory tract comprises of three regions: the upper airways, the conducting airways and the respiratory airways (Newman *et al.* 2009). The upper airways heat and humidify inhaled air; the conducting airways are responsible for the air transportation to the respiratory airways, where the actual gas exchange will take place. The lungs can also be divided according to Weiber model into 24 airway generations (Weiber 1963 in Newman *et al.* 2009) (Fig. 1). In this model the airways from 0-16 are considered as conducting airways and 17-23 as respiratory region composing of respiratory airways and finally ending into the alveolar sacs (generation 23) (Newman *et al.* 2009). The main function of the human lungs is to secure adequate oxygen levels in the blood circulation. In addition to this function it also acts as an excretion organ maintaining homeostasis. This includes the removal of excess carbon dioxide and when needed, some other unneeded and toxic volatile substances like inhalation anesthetics (Pleuvry *et al.* 2005) and ammonia (Tokuda *et al.* 2007).

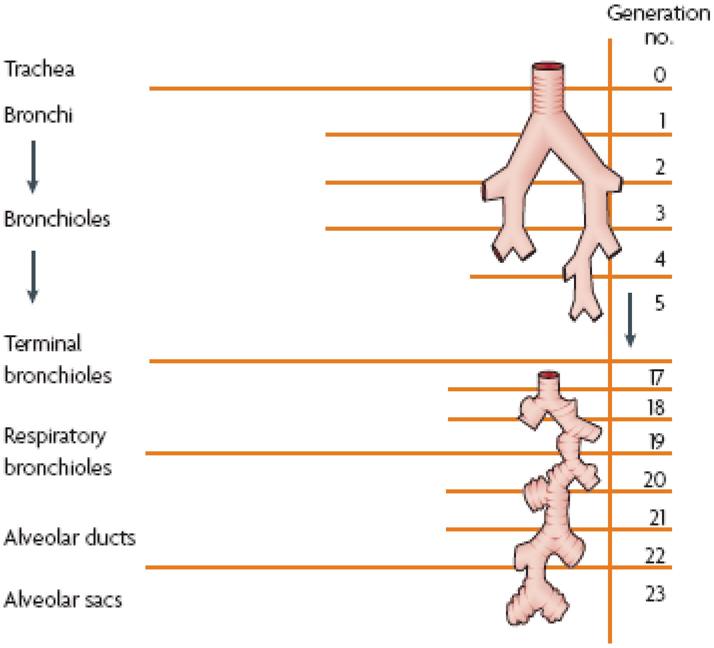


Figure 1. The Weiber model (Patton and Byron 2007, modified from the original)

From pulmonary drug delivery point of view the advantages are relatively large absorption area (approximately 100-190m$^2$ in an adult individual), good blood perfusion (approximately 5000ml/min, namely entire right sided cardiac output and partly also the left sided cardiac output), low metabolic activity and good permeability compared to other administration routes into the body (Newman *et al.* 2009). It also contributes to less systemic exposure and faster onset of drug action than for example oral route for lung diseases. Smaller metabolic exposure allows the use of lower effective dose, with even smaller systemic exposure and hence less side effects. Other advantages are the avoidance of injections and possibility to an alternative route for some drugs that are not absorbed via oral route.

The limitations for pulmonary drug delivery are accessibility as the respiratory airways are nearly always also the desired place for drug deposition (Newman *et al.* 2009) and individual variability and efficacy (Bechtold-Peters *et al.* 2007). Absorption of the drug depends on the drug aerodynamic behavior, breathing pattern of patients, timing of aerosol injection into the breathing cycle and airway anatomy and morphology. The lungs are a challenging route for drug delivery having commonly less than 20% efficacy in delivery technologies and even 500% individual variability. The API also has to reach the intended absorption site, to be absorbed and to avoid or delay the clearance of lungs (Newman *et al.* 2009). The clearance of lungs composes of: mucus movement towards throat, macrophages, enzymes, overall structure (turbulent flow, throat and tongue position) and coughing.

# 3 PARTICLE PROPERTIES RELEVANT FOR PULMONARY MEDICATION

A dry powder inhaler composes of the device and the powder blend. The powder blend composes of API and possible one or more excipients depending on the formulation approach used (Bechtold-Peters *et al.* 2007). Currently there are three main formulation approaches used: classical interactive mixtures, agglomerated powders or special production techniques.

The easiest way to formulate an inhalation powder is the classical interactive mixture approach (Bechtold-Peters *et al.* 2007). This includes a carrier substance, API and possibly additional excipients. A carrier substance is a larger-sized powder on to whose surface the smaller sized API will adhere (Newman *et al.* 2009). The most commonly used carrier is lactose monohydrate but in case of incompatibilities other crystalline sugars can also be considered (Bechtold-Peters *et al.* 2007). The challenges with this approach are dependent of API particle properties, carrier particle properties and blending related things.

Agglomerated powder approach is used for high drug doses and products intended for reservoir inhalers with good metering properties (Bechtold-Peters *et al.* 2007). This approach includes formulating the micronized API into agglomerated soft spheres with controlled spheronization process. These spheres may compose of solely the API or it may be combined with small amount of micronized lactose. The benefits of this approach are the lack of problems associated with classical ordered mixtures, such as the carrier material quality issues (Bechtold-Peters *et al.* 2007), and the better flow properties than micronized particles (Newman *et al.* 2009).

Special production techniques are used for high dose drugs and biotech compounds to produce diluent free directly used products (Bechtold-Peters *et al.* 2007). Typically the API and possible additives are spray-dried or freeze-dried to produce directly usable formulations. These types of formulations can for example be used for inhalation formulations (Bechtold-Peters *et al.* 2007, Sansone *et al.* 2009). Additives that stabilize API and minimize incompatibilities may include mannitol or low molecular weight polymers like dextran (Bechtold-Peters *et al.* 2007; Elversson and Millqvist-Fureby 2005b).

Regardless of the approach used there are some general requirements that can be listed for the inhalable particles that reach the lungs. These requirements are based on the limitations of the human body, issues related to the inhalation device functionality and the general stability (Newman *et al.* 2009). These particles can comprise of pure API or mixtures of API and excipients. These properties include: particle size, shape, surface morphology and solid state properties. The drug/carrier ratio and the presence of other components as well as hygroscopicity, electrostatic forces and overall stability are factors that contribute to the performance and viability of the formulation.

### 3.1 Particle size

In order to penetrate into the lungs a particle has to be small enough, namely preferably smaller than 5 μm in geometric diameter (Newman *et al.* 2009). This is because of the physical limitations in the human lungs. The lower limit of the particle size is governed by the increased exhalation tendency of particles smaller than 1 μm and the increased surface area that facilitates dissolution (Elkordy *et al.* 2012; Faiyazuddin *et al.* 2012). A decrease in particle size also decreases the transport capacity of the spray cloud as smaller particles contain less substance (Newman *et al.* 2009). Particles smaller than 1 μm are considered nanoparticles (1-0.01 μm, Kreuter *et al.* 1994 via Sham *et al.* 2004). They start requiring additional means like carrier particles (Sham *et al.* 2004) or formulation techniques (Tsapis *et al.* 2002) to be effectively transported to the lungs.

However, for pulmonary delivery geometric diameters can be slightly misleading. A better value to be used for an inhaled particle is the aerodynamic diameter ($D_a$) that describes the aerodynamic behavior of a particle (Newman *et al.* 2009). It can be seen from Equation 1 that aerodynamic diameter for a spherical particle is affected by physical diameter (D) and specific gravity (density relative to water, $\rho$) of the particle.

$$D_a = D\sqrt{\rho} \tag{1}$$

According to the Equation 1 particles that are denser than water (1 g/cm$^3$) behave as if they would be larger than their physical size and lighter particles behave as if they would be smaller than their physical size (Newman *et al.* 2009). A spherical particle with a physical diameter of 5 μm and density of 0.25g/cm$^3$ would behave aerodynamically similarly as 2.5μm diameter water sphere. Particles of low density are advantageous because with their low aerodynamic diameter and relative large volume they are able to disperse better and penetrate more efficiently into the deep lung (Platz *et al.* 2004). In addition they allow for escape from the natural phagocytic clearance in the lung and therefore increase bioavailability (Bechtold-Peters *et al.* 2007, Newman *et al.* 2009). This is due to their large geometric diameter that makes them too large for macrophages to engulf. These types of hollow particles can for example be produced with a spray dryer (Cheow *et al.* 2010).

Particle deposition in lungs is a result of three mechanisms: inertial impaction, gravitational sedimentation and Brownian diffusion (Newman *et al.* 2009) (Fig. 2). These mechanisms dominate different size bands. Inertial impaction dominates in the upper airways in areas where airstream changes its direction and can occur in inhalation or exhalation. The particle (between 1-10 µm) has too much inertia either because of large aerodynamic diameter or too fast speed and will not follow the airstream and hits the wall instead.

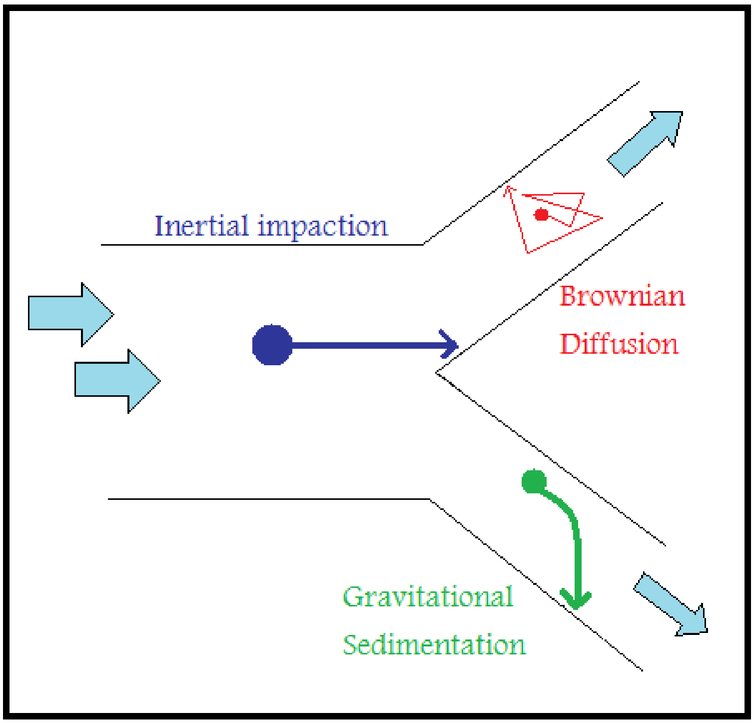


Figure 2. Schematic of the three major deposition mechanisms for a particle in the respiratory tract.

Gravitational sedimentation takes place in smaller conducting airways (Weibers model generations 8-16) and alveoli, where it is generally the dominant deposition process (Newman *et al.* 2009). It is caused by combination of gravitation and enough slow air flow during slow breathing or holding of breath. For example a 5µm particle with 1 g/cm$^3$ density has sedimentation rate of 0.74 mm/s causing it to deposit efficiently in 3 seconds breath holding in airways smaller than 2 mm diameter.

Particles with diameters less than 1 μm are most likely to deposit by Brownian diffusion, taking place mainly in alveoli (Newman *et al.* 2009). These small particles have insufficient inertia for inertial impaction and their settling velocity is too small for gravitational sedimentation. Brownian diffusion means that the particles move by collisions with gas molecules (Bechtold-Peters *et al.* 2007). The movement being irregular and unoriented will cause the particle to deposit after undefined amount of time depending on probability. The size band of around 0.5 μm is an exception whereas in addition to the other deposition mechanisms, it is also little impacted by Brownian diffusion. Below this size band deposition rises again due to Brownian diffusion and other additional effects (Newman *et al.* 2009). For example particles of 100 nm will deposit throughout the respiratory tract of which 20% will deposit in the alveolar region (Schmid *et al.* 2009 via Zhang *et al.* 2011). The nanosized particles could possibly be highly beneficial due to their delayed clearance and relatively larger surface if efficiently delivered to the lungs (Bhavna *et al.* 2009).

There are plenty of methods to measure the size of the inhalable particles. To measure the aerodynamic particle size, cascade impactors (CI:s) are preferred (Newman *et al.* 2009). A cascade impactor is a device that mimics the particle deposition in lungs as a function of their aerodynamic diameter, although geometric diameter is also postulated to contribute to the results (Vanbever *et al.* 1999). The general idea is to fit the inhalator into a linearly connected sieving system with generated air flow. There are several different designs available like Andersen Cascade Impactor (ACI), Next Generation Impactor (NGI) and Multistage Liquid Impinger (MLI) (Newman *et al.* 2009). The sources of errors in CI can be the wearing down of the device, wall deposition, blockage in the system and particle bouncing from surfaces.

To measure the geometric size a laser diffraction instrument or microscopic techniques can be used. The applicable range of a laser diffraction apparatus is around 0.1-1000 μm (Bechtold-Peters *et al.* 2007) but can even be 0,02-2000 μm (Rawle 2012). This makes it applicable for respiratory range sized particles (preferably 1- 5 μm diameters) (Bechtold-Peters *et al.* 2007). There are, however, a few limitations with the laser diffraction. The technology analyses a three dimensional particle and converts this knowledge into a one number that represents the dimensions of a particle (Rawle 2012). This description is valid only for a perfect sphere with a dimension of two times its range and not for a particle with random surface. Hence measured values are approximates. The increase in accuracy when the particles sphericity is increased is also supported by the studies of Martin *et al.* (2006). The microscopic techniques are considered accurate but skill demanding and time consuming (Newman *et al.* 2009). This is especially the case for traditional image analysis techniques. The microscopic devices include for example light microscopes and scanning electron microscopes (SEM).

Particle size is an important value when determining substances performance as a pulmonary aerosol, though for pharmaceutical powders particle size distribution is usually preferred as a describing factor over particle size. This is due to the common heterodisperse nature of pharmaceutical powders (Newman *et al.* 2009). The terms Fine Particle Fraction (FPF) and Fine Particle Dose (FPD) are used to describe the inhalation related performance of the powder. The former is defined generally as the percentage of the aerosol drug mass contained in particles smaller than about 5 μm and the latter is defined as the dose of drug depositing in a Cascade Impactor (CI) in particles with aerodynamic diameters less than a stated size or in a specific size range.

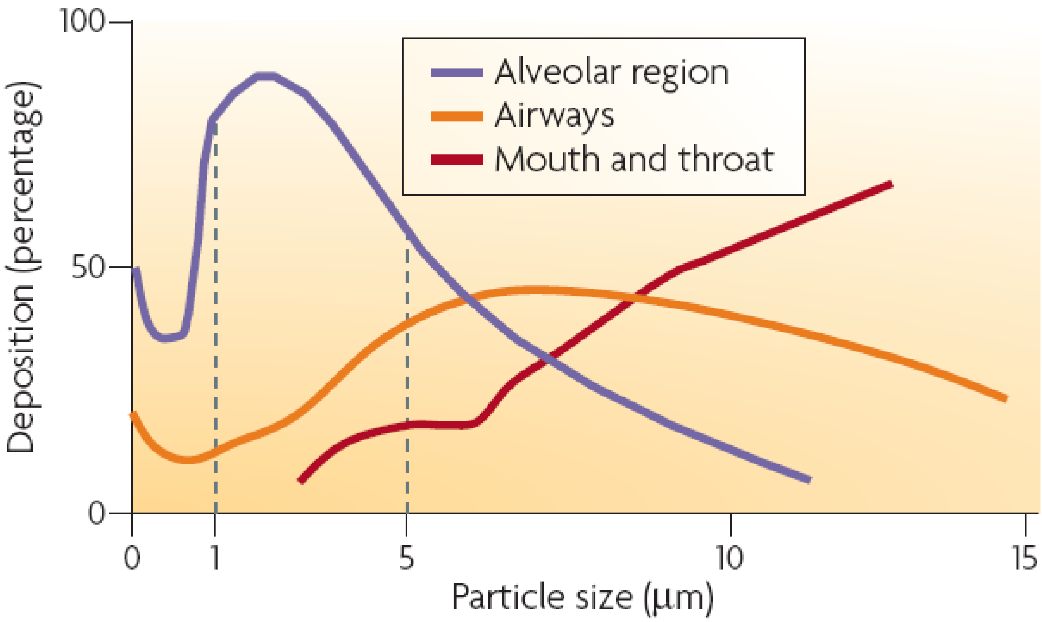


Figure 3. Deposition of places of different size brands in human respiratory tract (Patton and Byron 2007, modified from the original)

Different aerodynamic diameters can be used to target particles to different regions in the respiratory tract (Fig. 3) and some size bands (2-4 μm) even tend to be relatively independent on inhalation mode (Newman *et al.* 2009). To achieve best systemic delivery via lungs the low alveolar region is desired and particle sizes of probably 1-2 μm preferred (Chow *et al.* 2007). Different-sized particles might also be used to treat different kind of symptoms (Faiyazuddin *et al.* 2012). A relatively monodisperse particles have been produced with spinning top aerosol generator (Biddiscombe *et al.* 2003) and spray drying (Chawla *et al.* 1994; Cabral-Marques and Almeida 2009; Cheow *et al.* 2010; Xu *et al.* 2012). These types of particle size distributions would possibly allow more precise dosing of API.

### 3.2 Shape and surface structure

The diameter is a true definition only for spherical particles, whereas the non-spherical particles are represented with “apparent” diameters (Masters 2002). The apparent diameter is the mean distance between extremities of the particle measured through the centre of gravity of the particle. This, however, can make it difficult to evaluate and reproduce the results. For non-spherical particles the aerodynamic diameter is a value that defines the particle deposition mechanism (Chow *et al.* 2007) and hence is the most appropriate.

The Equation 2 presents an estimate of the aerodynamic diameter ($D_A$) for a non-spherical particle as the function of the following factors: the volume equivalent diameter (diameter of a sphere of equivalent volume, $D_V$), the particle density ($\rho$), the unit density (density of spherical calibration spheres,$\rho_0$) and the dynamic shape factor (defined as the ratio of the drag force on a particle to the drag force on the particle volume-equivalent sphere at the same velocity,$\chi$), (Chow *et al.* 2007). The shape factor ($\chi$) that is defined by size-measurements and approximations is seldom found useful (Masters 2002). A more useful technique is often some particle viewing technology (e.g. microscope) combined with in-house definitions.

$$D_a \cong D_V\sqrt{\frac{\rho}{\chi\rho_0}} \qquad (2)$$

It can be seen that decreasing the volume equivalent particle diameter ($D_V$), reducing the particle density ($\rho$) or increasing the particle dynamic shape factor ($\chi$) the aerodynamic diameter can be decreased to a more favorable state (Chow *et al.* 2007). According to the Equation 2 an optimal particle would be small, non-spherical and hollow. One possible method for production would therefore be a spray dryer with optimized parameters (Masters 2002).

The overall shape of a particle is a combination of the macroscopic shape and the surface structure. The shape is presented as the shape factor ($\chi$), but the surface structure is a considered as a combination of shape factor ($\chi$) and particle density ($\rho$), (Chow *et al.* 2007). Both of these have been noted to affect the aerosol performance of a powder although it has been suggested that this effect is dependent on the efficacy of the inhaler used (Chan 2008).

Many types of particles and surfaces have been produced and tested for inhalation purposes: round particles (Chawla *et al*. 1994), needle type particles (Larhrib *et al.* 2003), matrix type particles (Beinborn *et al.* 2012), hollow spherical particles (Vehring *et al.* 2007; Cheow *et al.* 2010), spherical porous particles (Vanbever *et al.* 1999; Healy *et al.* 2008; Nolan *et al.* 2009; Gad *et al.* 2012), rod shaped crystals (Gad *et al.* 2012), spherical crystal clusters, differently shaped crystalline habits (Kubavat *et al.* 2012), spiked spherical particles (Raula *et al.* 2009), rough-surfaced spherical particles (Adi *et al.* 2013). Of these produced particles, round particles (Chawla *et al.* 1994) performance was equal with the micronized particles. The needle type particles (Larhrib *et al.* 2003), hollow spherical particles (Vehring *et al.* 2007), spherical porous particles (Nolan *et al.* 2009) and spiked spherical particles (Raula *et al.* 2009) performed better than micronized particles. The rough-surfaced spherical particles (Adi *et al.* 2013) performed better than corresponding smooth particles. All results were not compared with the performance of other qualities but were instead verified to be suitable for inhalation purposes. There seem to be vast amount of different shapes to decrease the aerodynamic diameter of a particle. This indicates that currently there seems to be no one solution to amplify the aerosol performance by shape modification but several alternative solutions.

The increase in surface roughness (Vehring 2008; Kawakami *et al.* 2010), the introduction of surface structures (Raula *et al.* 2009; Ghoroi *et al.* 2013) as well as introduction of pores (Healy *et al.* 2008; Newmann *et al.* 2009; Nolan *et al.* 2009; Nolan *et al.* 2011) all aim to reduced number of surface contact points, hence interparticle cohesive forces are minimized. This has been noted to increase de-agglomeration and fine particle fraction (FPF) (Adi *et al.*

2008; Weiler *et al.* 2010; Adi *et al.* 2013). They all also beneficially lower the aerodynamic diameter. However, there might be a level of optimal surface roughness as is indicated by the study of surface asperities (Fig. 4), (Raula *et al.* 2009). Passing this optimal value might increase the interlocking of particles due to the increased shape fitting of corrugated surfaces (Raula *et al.* 2009; Weiler *et al.* 2010). These interlockings would be stronger for the more corrugated particles than for the less corrugated ones and could cause problems with aerosolisation.

Figure 4. Illustration of particle contacts with different surface structures. (Raula *et al.* 2009, modified from the original).

A preferred particle in respect to shape and surface structure is most likely a particle with small aerodynamic diameter and suitable amount of surface roughness (Weiler *et al.* 2010). In addition to these factors there are plenty of other factors that should be studied more closely in order to define the effect of the overall shape on aerosol behavior. These include the preferential particle orientation and characteristic particle rotation time that have been proposed to be important factors (Shekunov *et al.* 2007).

### 3.3 Particle composition

Dry powder inhalation formulation can be composed of the plain API (Healy *et al.* 2008; Sansone *et al.* 2009) or API combined with different excipients (Raula *et al.* 2009; Kubavat *et al.* 2012) or together with different APIs and excipients (Traini *et al.* 2012). The formulations containing more than one substance can either be formulated into same particles (Raula *et al.* 2009; Kumon *et al.* 2010) or mixed together to form interactive powder mixtures (Kubavat *et al.* 2012).

Sole API particles have the benefit of not exposing the body to unneeded substances like excipients, part of which can theoretically be harmful (Healy *et al.* 2008). Also a higher payload of drug may be a more efficient way to deliver the drug especially if larger doses are needed (Muttil *et al.* 2007). The challenges remain in the production and process optimization (Sansone *et al.* 2009). The possible production can be performed for example with spray drying (Bechtold-Peters *et al.* 2007; Healy *et al.* 2008; Nolan *et al.* 2009; Nolan *et al.* 2011; Sansone *et al.* 2009), controlled spheronization or freeze drying (Bechtold-Peters *et al.* 2007).

More often the API is combined with excipients or other APIs to enhance its performance or stability (Muttil *et al.* 2007). They can also broaden the type of substances and the geometric size range that can be used. For example the right excipients have made it possible to deliver large molecules like insulin (6000 Da) (Bechtold-Peters *et al.* 2007) and small nanoparticles to the lungs (Sham *et al.* 2004; Bhavna *et al.* 2009; Beck-Broichsitter *et al.* 2012). Examples in the protein stabilization include the addition of surfactants or simple sugars like mannitol into the formulation (Millqvist-Fureby *et al.* 1999). Surfactants like Tween 80 can displace the protein from the surface of the atomized droplet and thus preserve its activity. Simple sugars can improve stability and aerosol performance, depending on their physical state and concentration.

The different components in the formulation can be applied to form layers over one another (Elversson and Millqvist-Fureby 2005b; Elversson and Millqvist-Fureby 2006; Buttini *et al.* 2008b; Albertini *et al.* 2008) (Fig. 5, c), to form particles with a blend composition (Bosquillon et *al.* 2001; Kumon *et al.* 2010; Traini *et al.* 2012) (Fig. 5, a), to be mixed into an interactive or ordered mixture (Harjunen *et al.* 2002b) (Fig. 5, b) or to be a combination of some of the presented methods (Traini *et al.* 2012) (Fig. 5, d). The type and amount of the excipients and the formulation type has been noted to affect considerably on the aerosol performance of the powder (Bosquillon et *al.* 2001; Bechtold-Peters *et al.* 2007).

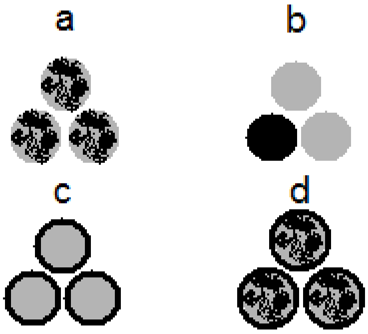


Figure 5. Schematic drawing to illustrate the different component mixtures.

In an interactive mixture formulation the excipients crystallinity has been noted to increase the stability and flowability (Harjunen *et al.* 2002b). Size distribution that includes finer fractions has been noted to increase the emitted drug dose possibly due to the lower adhesion tendency (Harjunen *et al.* 2002b; Guenette *et al.* 2009; Kaialy*et al.* 2010). An increase in surface roughness has been noted to decrease the emitted drug dose. The shapes of needle (Kaialy *et al.* 2010) and pollen (Hassan and Lau 2011) have been tested as carrier particles with good results. As for the whole formulation type, decrease in density seems to also decrease the emitted dose of the API (Harjunen *et al.* 2002b).

Combining all the components into blend particles seem to be an efficient way to deliver drugs (Muttil *et al.* 2007; Kumon *et al.* 2010), produce high fine particle fraction and improving dose uniformity (Tajber et al. 2009b). The addition of excipients has also been noted to extend the release of API (Muttil *et al.* 2007; Beck-Broichsitter *et al.* 2012). Another solution to perfect the design seems to be the addition of molecules that spontaneously accumulate on the particle surfaces, e.g. sodium dodecyl sulphate or PVP to modify it (Buttini *et al.* 2008b; Kawakami *et al.* 2010).

The excipients used in a DPI formulation can include crystalline sugars (lactose, glucose, trehalose, sucrose, raffinose, mannitol), polymers (dextran, inulin) (Bechtold-Peters *et al.* 2007), fluorocarbons, lung surfactant dipalmitoyl phoshatidylcholine (DPPC), fumaryl diketopiperazine (Newmann *et al.* 2009), poly lactic acid (LPA) (Muttil *et al.* 2007), poly vinyl alcohol (Buttini *et al.* 2008b) and others. Currently lactose is considered as the golden standard for inhalation excipient due to its inert nature, low cost and extensive use (Bechtold-Peters *et al.* 2007). Especially it is used as a carrier in interactive powder mixtures.

It appears that the larger amount of surfaces the excipient covers and the more excipient is used the more effect it has on the quality of the powder (Bechtold-Peters *et al.* 2007; Kawakami *et al.* 2010). The use of a multitude of excipients adds another variable that may be difficult to evaluate without experimental data on the specific case. Large amounts of excipients also make the emitted dose (ED) less dependent on the turn down ratio of the inhaler since the emitted dose is defined as the mass of API exiting the mouthpiece of an inhaler each time the inhaler is used (Newman *et al.* 2009).

## 3.4 Solid state properties

A solid mass of API molecules packed together can form a three-dimensional long-range order that is considered as a crystalline structure or they can form an unoriented mass that is considered as an amorphous structure (Hancock and Zografi 1997). However, typically the amorphous structure forms short range orders over few molecular dimensions. It is possible that an API may form more than one different crystalline structure (polymorphism), each of which can in turn form different crystal shapes (crystal habits) (Stieger and Liebenberg, 2012) (Fig. 6).

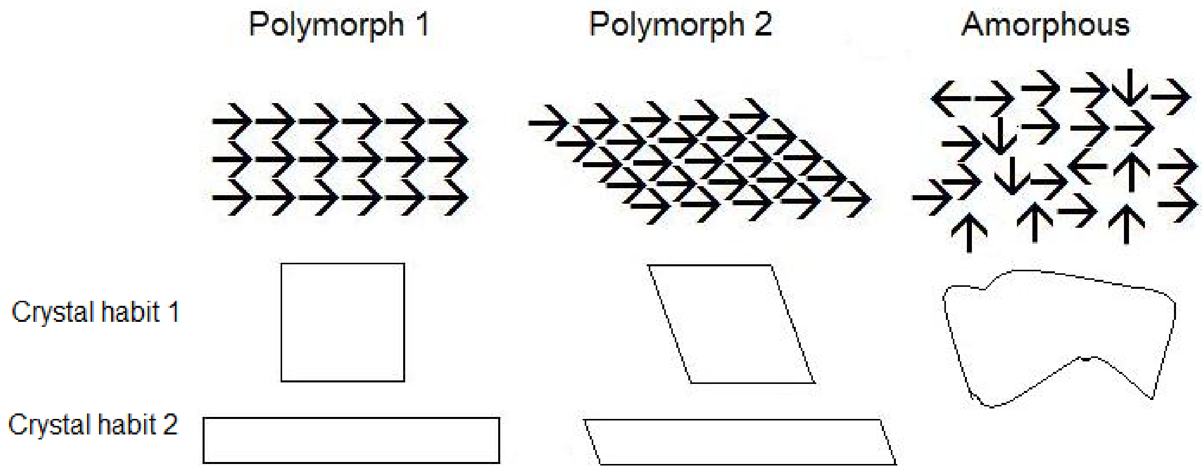


Figure 6. Schematic representation of different solid state structures and crystal habits.

As the crystallization is a process it takes time to be completed and is affected by many factors, such as temperature, saturation level and additives (Stieger and Liebenberg, 2012).
The crystallization rate probably has optimal values below the melting point of a substance. Although rapid cooling and rapid evaporation have been noted to increase nucleation of molecules, which is the perquisite for crystal growth, processes like rapid precipitation from solution are said to promote formation of amorphous structure. Spray drying is an example of a rapid precipitation process from solution and it is said to produce amorphous quality material (Hancock and Zografi 1997). However, it is claimed that the level of crystallization may be adjusted by controlling the operation conditions (Chiou *et al.* 2008). Other examples to produce amorphous materials in pharmaceutical production include: vapour condensation, supercooling of melt and milling and compaction of tablets (Hancock and Zografi 1997).

Figure 7 shows the supercooling of melt as a function of temperature, volume and enthalpy. The temperatures ($T_K$) ($T_g$) ($T_m$) are Kauzmann temperature, glass transition temperature and melting point. The $T_K$ is the theorethical limit for the $T_g$ (Ediger *et al.* 1996), the $T_m$ is the temperature where the crystalline/liquid transition takes place and the $T_g$ is the temperature for liquid/amorphous transition (Hancock and Zografi 1997). Of these values the value $T_g$ is not considered an exact value as it is found dependent on the thermal history of the sample and experimental conditions (Baird and Taylor 2012). It is rather considered as an indication of the area for transition region. The measurement of $T_g$ may be challenging (Nolan *et al.* 2011).

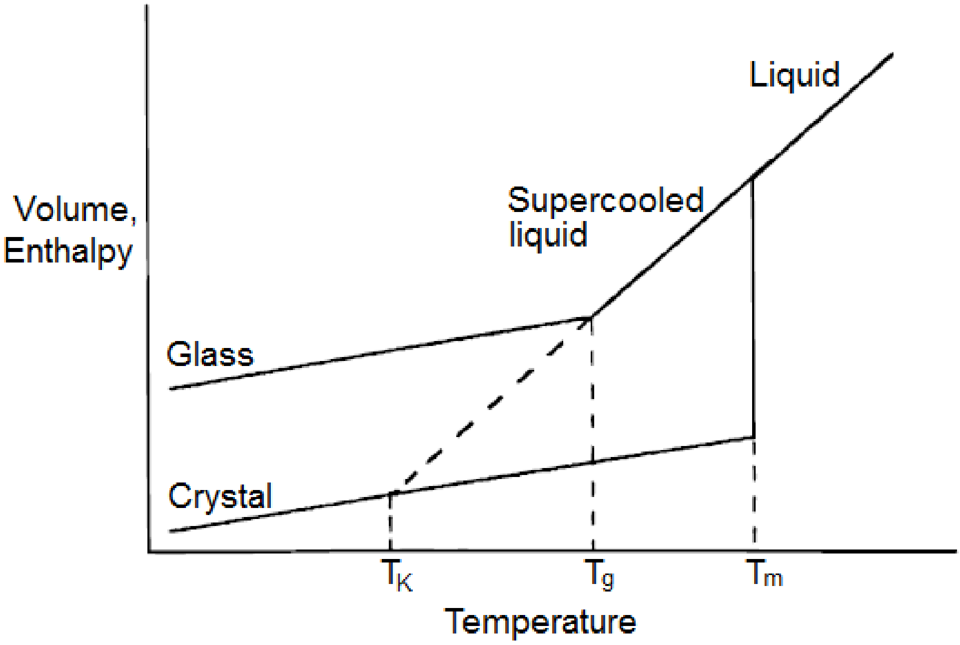


Figure 7. Schematic representation of the supercooling of a melt (Hancock and Zografi 1997, modified from the original).

When a liquid substance (Fig. 7) is cooled it first reaches the $T_m$ and starts to crystallize and a decrease is seen in both volume and enthalpy (Hancock and Zografi 1997). Crystalline structures are considered as less energetic and highly stable when compared to amorphous structures. The possible existence of polymorphs adds another variable as each of them has unique physical properties and stability (Stieger and Liebenberg, 2012). The existence of different energy states creates a possibility for the amorphous product and other polymorphs for a transformation towards the most stable polymorph, if given the proper conditions. Therein the choice between the known polymorphs is often a compromise between stability and solubility to secure the best properties for pharmaceutical production.

If the cooling in Figure 7 is done rapidly the system may pass the $T_m$ and become supercooled liquid (Hancock and Zografi 1997) or “rubbery” type material (Baird and Taylor 2012). When the cooling is continued further to $T_g$ many changes are observed in the physical properties of the cooled material. These include changes in viscosity, density, heat capacity, X-ray diffraction and diffusion. This new glassy state of material with the structural characteristics of a liquid but with considerably higher viscosity is considered as amorphous material (Hancock and Zografi 1997). Amorphous form is typical for polymeric molecules, large peptides and it can occur for small inorganic and organic molecules as well. The low molecular weight pharmaceuticals may form more fragile glasses than polymers (Craig *et al.* 1999).

As the amorphous material is relatively high energetic, a chance of crystallization is always present in handling and storage (Hancock and Zografi 1997), although amorphous materials are proposed to remain stable at their Kauzmann temperature or below it (Corrigan *et al.* 2004). The considerably greater hygroscopicity of the amorphous material is further influencing its stability when compared with its crystalline counterparts (Nakai *et al.* 1977, Pikal *et al.* 1978 in Ahlneck and Zografi 1990). The increase in water content increases molecular mobility by reducing hydrogen bonding between adjoining molecules and decreases the value of $T_g$ (Franks 1982; Levine and Slade 1987; Levine and Slade 1988; Slade and Levine 1988 in Ahlneck and Zografi 1990) (Fig. 8). This increased molecular mobility in metastable areas like amorphous regions can promote chemical degradation and solid-state phase changes, such as crystallization (Ahlneck and Zografi 1990).

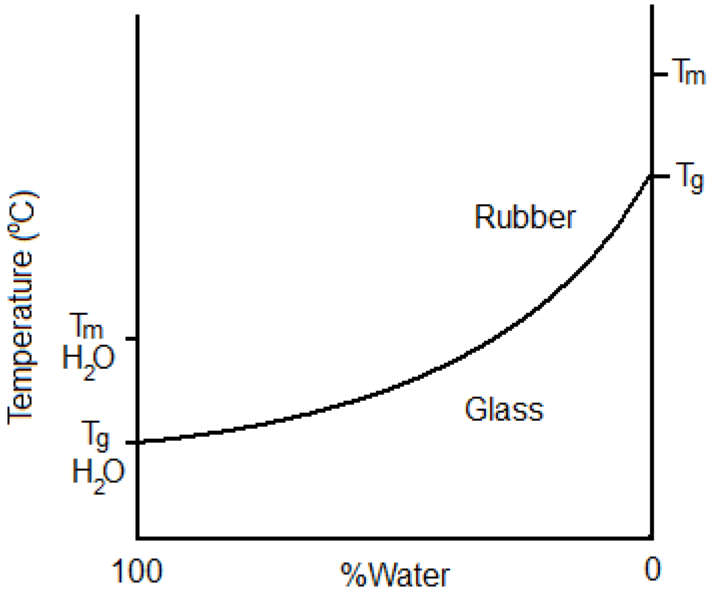


Figure 8. Schematic representation on the effect of water on the Tg of the solute (Ahlneck and Zografi 1990, modified from the original)

When producing crystalline material from solutions the fundamental driving force for crystallization is the chemical potential between the solution and the solid phase (Stieger and Liebenberg, 2012). This may also be expressed as supersaturation that is a solution with higher concentration of solids than in saturated solution at that defined temperature. Supersaturation is not a stable state and aims for equilibrium via free energy reduction which can be provided for example via crystallization. The crystallization from solution is currently not fully understood, especially the formation of nuclei (Chen J. *et al.* 2011). There are two suggested models: Classical nucleation model and Two-step nucleation model (Fig. 9). In the Classical model the molecules start building nuclei due to the fluctuations and this eventually may grow up to be a crystal, whereas in the Two-step model the molecules form larger clusters and later restructure to a more compact structure. The crystallization from solvent often leads to an API-solvate that is a metastable solid state of the solid molecules with solvent molecules in their crystal lattice (Stieger and Liebenberg, 2012). Solvates can sometimes be used for further development although this is often restricted by the possible existence of toxic solvent molecules in crystal lattice. The solvents may be removed from solvates although this may cause stability issues.

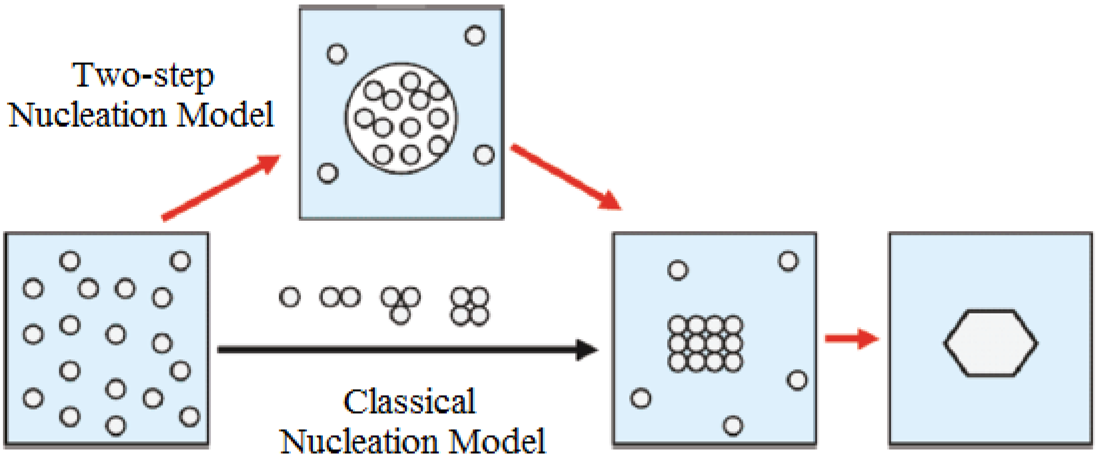


Figure 9. The two nucleation models (Chen J. *et al.* 2011, modified from the original)

The nucleation of molecules and crystal growth rate are dependent on the level of supersaturation (Stieger and Liebenberg, 2012). An increase in it leads to increased crystallization speed and decreased crystal size, though excessive increase may lead to amorphous material (Hancock and Zografi 1997). Some substances (like sucrose) can form supersaturated solutions of high stability that may postpone solidification (Elversson and Millqvist-Fureby 2005a). Supersaturation and therein crystallization may be achieved either by increasing the solute concentration or by decreasing the solute solubility or by combining both of the methods. Increase in solute concentration can be done by for example by evaporation of solvent and the decrease in solubility by cooling, addition of antisolvent, pH change or the addition of ions that participate in the precipitation of the solute. Interestingly, Kaialy and Nokhodchi (2012) reported that in antisolvent crystallization less saturated solutions produce higher fine fractions and less amorphicity in the final product.

The solid state of the API is an important factor for inhalable small-sized powders due to the effects it has on stability and the performance of the processed API. This makes the decision of solid state a case specific challenge. The constant finding of new ways to produce new polymorphs (Stieger and Liebenberg, 2012) and the finding of new ways to stabilize amorphous structures increases the alternatives used for pharmaceutical production.

## 3.5 Hygroscopicity

One of the duties of the upper airways is to heat and humidify the inhaled air to more than 99% relative humidity and body temperature (Newman *et al.* 2009). In such conditions solid hygroscopic materials may quickly absorb water and grow in size whereas non-hygroscopic materials are mostly unaffected until a certain point is reached (Chew and Chan 2002, Columbano *et al.* 2002) (Fig. 10). The absorption of water on the surface of a particle may also enhance the adhesion force between the particles (Kawakami *et al.* 2010) and crystallization tendency (Ahmed *et al.* 1996).

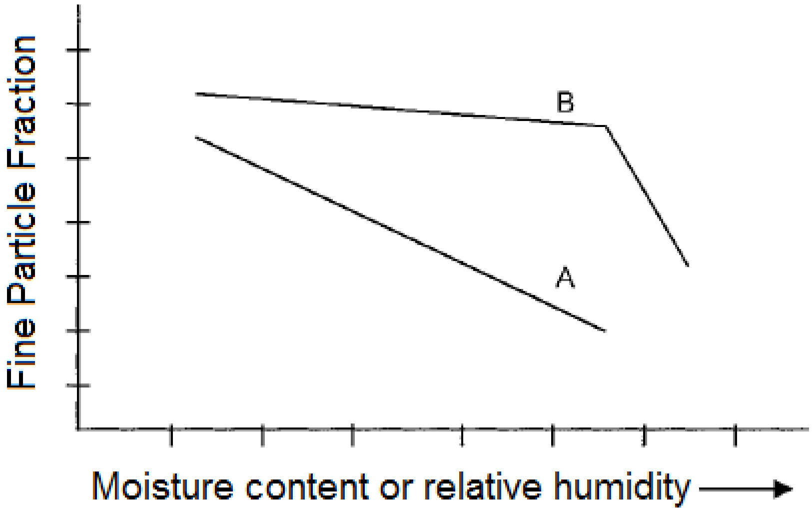


Figure 10. Schematic drawing of the effects of moisture content or relative humidity on the fine particle fraction of different types of powders. Line A represents a hygroscopic powder and line B represents a non-hygroscopic powder (Chew and Chan 2002, modified from the original).

The water-induced particle growth might decrease exhalation and increase earlier lung deposition (Newman *et al.* 2009). The result is that the more hygroscopic substances deposition location and effect may be altered more. This would be especially critical for systemic delivery that is considered to be most efficient in the alveolar region (Chow *et al.* 2007). It is also suggested that the smallest particle fractions would be the most sensitive particle fractions for moisture (Guenette *et al.* 2009; Crisp *et al.* 2010).

## 3.6 Interparticulate interactions

The performance of a DPI formulation is dependent on the interparticulate forces that should be optimized (Newman *et al.* 2009). They should be strong enough to promote stability during storage and handling but weak enough to allow formulation de-aggregation and dispersion during inhalation. There are several forces that effect the interactions between particles:

1. capillary forces
2. electrostatic forces
3. Van der Waals forces
4. mechanical interlocking

These forces are dependent on the environmental factors, material properties and processing conditions (Newman *et al.* 2009). The Van der Waals forces and mechanical interlocking are effective in short range contact points. The latter is dependent on the surface and particle shapes. Powder formulations are particularly affected by the capillary and electrostatic forces. Capillary forces are a result of the presence of water and can be minimized for example by individual blister packaging or with the help of desiccant. Electrostatic charging in powders is mostly caused via triboelectrification due to the contact between different surfaces and therein is involved nearly every process that involves powder handling (Karner and Urbanetz 2011). It can be a nuisance causing material losses in packaging and processing but also a good instrument in modifying the characteristics of a powder. Mixing two oppositely charged powders, ordered mixtures can be created (Linsenbühler and Wirth 2005). The electrostatic charge of an aerosol can be modified by changing the API/excipient ratio (Karner and Urbanetz 2013), the size of particles (Murtomaa *et al.* 2004; Karner and Urbanetz 2013), presence of carrier fines (<40mm) and aerosolization airflow (Karner and Urbanetz 2013).

The interparticulate forces can be divided in cohesive and adhesive forces (Newman *et al.* 2009). Cohesive forces are attractive forces between similar molecules and adhesive forces between different molecules. The cohesion between particles in a powder mixture can be modified by changing the API/excipient ratio (Behara *et al.* 2011) or the size of particles (Guenette *et al.* 2009). This is supported by the results of Karner and Urbanetz (2013). Adhesive forces can be manipulated by changing the relative size of the interacting surfaces (Katainen *et al.* 2006; Thi *et al.* 2008) and the relative humidity (Zhu *et al.* 2008). For an interactive mixture formulation it was first noted that a minor increase in relative humidity decreases adhesive forces, increases FPF and ED. This was thought to be caused by dissipation of electric charges due to the increased moisture. An extensive increase in relative humidity on the other hand starts to increase adhesive forces and decrease FPF and ED. This is thought to be caused by the increase of capillary forces via liquid bridges.

### 3.7 Stability

A formulation must be stable for the labeled shelf life and an inhalation product is no exception (Newman *et al.* 2009). The stability of the produced formulation must be adequate in manufacturing to sustain possible further processing, storing and packaging. In an inhalator the formulation must sustain handling, usage and environmental factors like temperature and humidity (Newman *et al.* 2009). Finally in the human respiratory tract the formulation must sustain that environment adequately to allow the designed drug dosing (Bechtold-Peters *et al.* 2007).

DPI formulation is considered to be reasonably stable when compared to liquid formulations and it has no requirements for sterile manufacturing (Newman *et al.* 2009). Therefore it is even used as a way to stabilize macromolecules (Bechtold-Peters *et al.* 2007; Newman et al. 2009) and minimize microbiological contaminations (Bechtold-Peters *et al.* 2007). The stability also presents challenges as the drug and carrier agglomerates separation in carrier formulations is partly dependent on the inspiratory effort from the patient (Newman *et al.* 2009). The intact remaining part of the agglomerates deposits in the upper airways and does not necessarily provide the wanted pharmacological effect. This and the possible moisture sensitivity of the powder are among the greatest challenges with DPI formulation stability. While water alone can promote chemical and physical reactivity (Ahlneck and Zografi 1990), this is increased even further when combined with temperature increase (Burnett *et al.* 2004). Promoted chemical and physical reactivity may cause solid state transitions like crystallization. Different storage temperatures and humidities can facilitate growth of different polymorphs (Bianco *et al.* 2012).

## 4 SPRAY DRYING

A basic spray dryer composition is illustrated in Figure 11 (Büchi 2012). The spray dryer is used to process food, biochemical compounds and pharmaceutical substances (Masters 2002). The reason for such popularity is its relative simplicity, availability, applicability and ease of operation. In the field of inhalation particle processing however, it is a rather new technology.

This is because of the relative small particle size and size distribution that require considerable amount of process optimization.

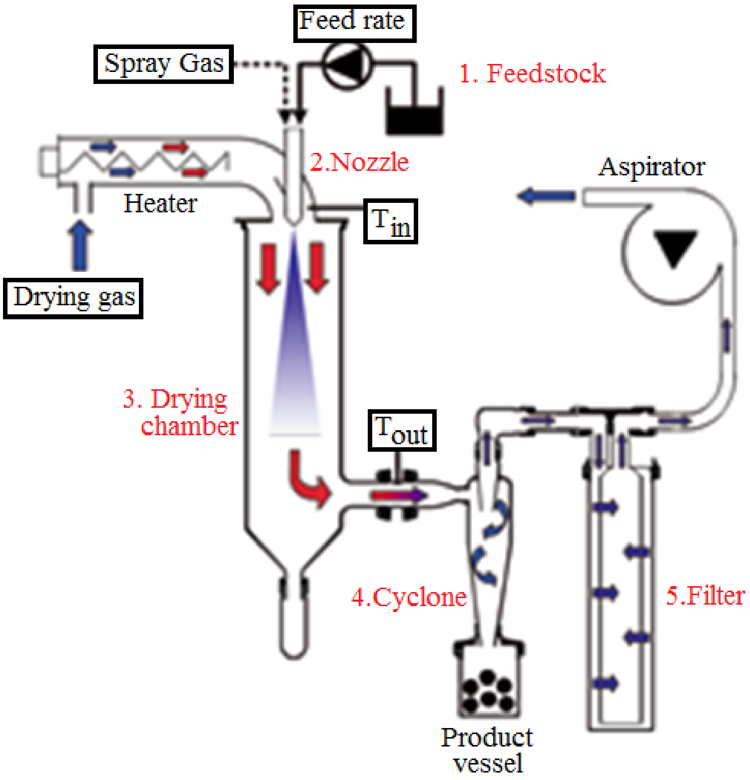


Figure 11. Technical drawing of the B-290 spray dryer. (www.buchi.comTMS, modified from the original) The prepared mixture to be spray dried composes the feedstock (1.). From the feedstock the mixture is pumped to the nozzle (2.), from where it is sprayed to drying chamber (3.). The final product is collected mainly in the cyclone (4.) and partly in the filter (5.)

The spray drying cycle can be open, closed or semi-closed (Masters 2002). Open cycle means that the drying medium is air that is released to atmosphere after passing through the process. The closed cycle system is used to prevent fire and explosion risks (e.g. flammable solvent or solute), environmental and working area toxicity (toxic solvent or solute) or to prevent contact with oxygen (oxidation). Closed cycle uses some inert gas (e.g. nitrogen) that is recycled during the process. A semi-closed cycle is used to partially minimize either fire risk or exhaust air toxicity. This is achieved by lowering the oxygen concentration of the drying medium or in the latter case by minimizing the exhaust air by recycling. Spray drying process can also meet aseptic/hygienic processing conditions if needed.

To produce crystalline particles of inhalable size in a single process would be beneficial for its stability (Stieger and Liebenberg, 2012) and rapidity (Masters 2002). Spray drying is a rather quick method and is known to produce particles of inhalable size, though the quality is often amorphous (Masters 2002). The reasons for amorphous product are said to be the very fast precipitation of the material and the lack of an isolation time. To produce more crystalline material one has to change the parameters used (Chiou *et al.* 2008). In a spray dryer both the formulation parameters and the process parameters contribute to the quality of the product (Chan and Chew 2003). In studies conducted by Tajber *et al.* (2009b) even 7-fold increases in respirable fraction (< 6.4μm) have been noted due to the process parameter optimization. For a new processed substance it may be challenging to utilize any former process parameter data and therefore experimental work is unavoidable (Gallo *et al.* 2011).

## 4.1 Mixture composition

Virtually any pumpable mixture can be used for spray drying (Masters 2002). This limits the mixture to be composed of at least one liquid component mixed with other liquid or solid components. The liquid component is usually water but non-aqueous volatiles, like organic solvents, can be used (Masters 2002). In some cases the feed can also be molten. The important parameters in the mixture are the number and amount of components, their contribution to the mixture (Bosquillon *et al.* 2001; Traini *et al.* 2012) and the solubility of the solid components in the liquid mixture (Gilani *et al.* 2004) as the behavior of solution and suspension differs in spray drying (Masters 2002).

The solid concentration in the mixture is a significant parameter (Cheow *et al.* 2010). An increase in it has been noted to increase several factors including: particle size (Elversson *et al.* 2003; Corrigan *et al.* 2004; Mosen *et al.* 2004; Elversson and Millqvist-Fureby 2005a; Maury *et al.* 2005; Sansone *et al.* 2009; Amaro *et al.* 2011; Gallo *et al.* 2011; Buchi process parameters guide 2012), yield, width of the particle size distribution (Corrigan *et al.* 2004), density (Elversson *et al.* 2003), surface roughness (Gad *et al.* 2012) and the thermal efficiency of the spray dryer (Masters 2002). Decreases have been noted in the humidity of the final product (Maury *et al.* 2005; Amaro *et al.* 2011; Buchi process parameters guide 2012). Concentration is a major factor for crystallization (Stieger and Liebenberg, 2012) although the effect of concentration on solid state has been noted to depend on the type of the spray-drying cycle (Bianco *et al.* 2012). It is also claimed that high concentrations might slow down crystallization due to the lower initial moisture and higher heat capacity (Chiou and Langrish 2008). Lower moisture would not decrease the $T_g$ effectively and higher heat capacity would slow the heating of droplets to more crystallization favoring temperatures.

The lower solubility of the solute is also said to increase particle size (Elversson and Millqvist-Fureby 2005a). The pH of the feed is found to be a significant factor when the feed has pH specific components and it has effects on particle size distribution of the product (Cheow *et al.* 2010).

The type of feed used dictates the performance in the spray dryer (Masters 2002). Generally droplets containing suspended solids tend to dry faster than solution droplets containing solids or emulsion droplets. This is caused by the differences in moisture migration. Interestingly, yield is noted to improve when using solutions instead of suspensions with the same amount of solids though the change in solvent ratio might have an effect as well (Sansone *et al.* 2009). The use of a suspension may facilitate nanoparticle production in spray drying (Bhavna *et al.* 2009). An increase in nanoparticle size and suspension concentration was noted to increase the size of produced nanoparticle polymer composites and an increase in molecular weight of the polymer seems to increase mean particle size (Beck-Broichsitter *et al.* 2012). An increase in concentration of suspension was also noted to affect the shape of particles and decrease the uniformity of the particle size distribution (Cheow *et al.* 2010). The addition of solids over the solubility limit of the solution does not linearly change the solid state of the final product (Chidavaenzi *et al.* 1997).

The type and the amount of the excipients seem to affect greatly on the quality and performance of the formulation (Bosquillon *et al.* 2001) especially on shape of the particles (Corrigan *et al.* 2004). An addition of polymers was noted to increase surface roughness (Kawakami *et al.* 2010) whereas an increase in colloidal silicon dioxide was found increasing flowability properties, compactability and stability (Gallo *et al.* 2011). When spray drying protein products, the density of particle was noted to increase (Maltesen *et al.* 2008) and particle corrugation decrease when protein concentration is increased (Adi *et al.* 2008). The overall effect of the addition of proteins and lipids in a formulation is a decrease in density whereas the increase in sugar concentration led to an increase in bulk density (Bosquillon *et al.* 2001).

The performance of lactose in an Andersen Cascade Impactor (ACI) was considered better than that of mannitol and trehalose when combined with dipalmitoyl phoshatidylcholine (DPPC) and was further improved with the addition of albumin. Many carbohydrates like isomalt, lactitol, maltitol, xylitol and sorbitol may be challenging to process with spray dryer

(Gonissen *et al.* 2007). With the Gordon-Taylor (Gordon and Taylor 1952 in Corrigan *et al.* 2004) equation it seems possible to predict the stability and formation probability of an amorphous structure in composites (Corrigan *et al.* 2004). The $T_g$ of the composite should be high enough to yield Kauzmann temperature higher than storage temperature in order to be stable. A crystalline excipient has been noted to produce porous particles whereas amorphous excipients produce hollow particles (Elversson and Millqvist-Fureby 2005a). The addition of pore formers, such as ammonium carbonate is sometimes preferred to produce porous particles (Healy *et al.* 2008, Nolan *et al.* 2009). Leucine can be used as an additive to lower cohesiveness and thereby increase the yield and aerosol performance (Boraey *et al.* 2012).

Spray drying can be used to crystallize substances *in situ* from solvent mixtures (Mezzena *et al.* 2009; Bianco *et al.* 2012). The level of crystallization in water soluble material was increased when the water concentration was decreased (Harjunen *et al.* 2002a; Gilani *et al.* 2005; Bianco *et al.* 2012) and when the concentration of solid material was increased (Chidavaenzi *et al.* 1997). Ethanol soluble materials seem to show similar trend as less crystalline materials are produced as the ethanol concentration increases though there are contradictory results (Gad *et al.* 2012). The use of co-solvent system (Harjunen *et al.* 2002a; Gilani *et al.* 2005; Bianco *et al.* 2012; Gad *et al.* 2012), adding excipients (Carr *et al.* 2011) and combinations thereof have been used to produce more crystalline solution. Crystallinity can also be lowered by adding different substances to the mixture (Traini *et al.* 2012). A more crystalline product can also be obtained by spray drying precrystallized mixtures (Rasenack *et al.* 2002).

The use of organic solvents instead of water may decrease energy consumption provided that the boiling point of the used organic solvent is lower than that of water (Buchi process parameters guide 2012) and may facilitate dissolution of less water soluble components (Muttil *et al.* 2007; Boraey *et al.* 2012). Organic solvents that reduce surface tension may cause reduction in particle size (Buchi process parameters guide 2012; Bürki *et al.* 2011) and may increase FPF (Sansone *et al.* 2009). As the ethanol concentration is increased there is no noted further change in particle size but the density of powder will increase (Bosquillon *et al.* 2001) and particles seemed to be more spherical (Gad *et al.* 2012). The effect of the ethanol/water ratio on particle shape seems to be dependent on the solubility of substances in different tested solvent mixtures. The roundness of the particles produced by Harjunen *et al.* (2002a) increased with water soluble substance when moved towards more water abundant solutions and Gad *et al.* (2012) produced rounder particles with ethanol soluble substance from ethanol abundant solutions. The increased solubility may facilitate solid state change of a particle but not always, since Gad *et al.* (2012) produced crystalline quality in all experiments. Apparently also the particle size change effected by ethanol concentration is dependent on various things as Sansone *et al.* (2009) noticed. Increased ethanol concentrations with ethanol soluble substance produce smaller particles. The use of organic solvent and water mixtures can be beneficial especially when the aim is to produce small porous particles as it is claimed that the mixing ratio may adjust the pores (Nolan *et al.* 2009). A mixture of water and methanol is preferred over a mixture of ethanol and water due to the narrower size distribution and more uniform shape produced (Healy *et al.* 2008; Nolan *et al.* 2009) although other solvent mixtures can be used as well (Nolan *et al.* 2011).

## 4.2 Feeding phase

In the feeding phase the adjustable properties are: possible pretreatments before pumping the prepared liquid feedstock to the nozzle, pump rate and physical variables like hose length and material. To transfer the feed from feedstock to the nozzle a transfer pump, such as rotary, centrifugal (Masters 2002) and peristaltic, can be used. The pumping is generally not that demanding in spray drying unless very high pressure nozzle atomization is used. The feed pretreatment can for example be mixing (Masters 2002; Stieger and Liebenberg 2012), heating (Masters 2002), adding of gas, concentrating of feed, filtering or mixture thereof.

Mixing is introduced to maintain homogeneity (Galloe *et al.* 2011; Stieger and Liebenberg 2012), but it also has some complex effects on nucleation and crystal growth in the mixture (Stieger and Liebenberg 2012). The mixing of a constant supersaturated solution with no crystals yet present decreases the induction time (time when crystals first appear) with the increase of stirring speed till critical speed is reached. This is due to the active creation of secondary nuclei by crystal impacting on other crystals, vessel or impeller. The increased creation of nuclei also leads to decrease in the ultimate crystal size of the product and apparently can affect the chiral symmetry of the product. The crystal growth is also stirring intensity dependently limited.

Heating is added to reduce feed viscosity and to prevent feed crystallization (Masters 2002) but it also effects the saturation (Stieger and Liebenberg 2012). Lower viscosity in feed is sometimes desired as it tends to produce homogenous sprays and smaller particle size (Masters 2002). The effect of heat on crystallization tendency might be related to the materials used as Alves and Santana (2004) found that an increase in temperature might increase crystallization propensity. Gas addition can be included to decrease the bulk density and alter the morphology (Masters 2002; Steckel and Brandes 2004). The feed concentrating is done to increase density (Masters 2002) and combining it with an increase in feed rate is said to increase crystallinity (Alves and Santana 2004).

An increase in the feed rate increases the amount of solvent to be evaporated and material to be dried. It also increases the spray angle, bulk density of the product (Masters 2002), the droplet size of the spray (Maury *et al.* 2005; Buchi process parameters guide 2012), particle size, humidity of the final product (Masters 2002; Maury *et al.* 2005; Tajber *et al.* 2009b; Gallo *et al.* 2011; Buchi process parameters guide 2012; Shi *et al.* 2012), but decreases the outlet temperature (Maury *et al.* 2005; Maltesen *et al.* 2008; Amaro *et al.* 2011; Buchi process parameters guide 2012). An increase in flow rate has also been noted to increase FPF of the powder (Boraey *et al.* 2012).

At higher liquid feed rates the atomization becomes incomplete, droplet size distribution becomes wide (Masters 2002), drying chamber becomes wetted (Cheow *et al.* 2010) and yield drops (Tajber *et al.* 2009b; Cheow *et al.* 2010; Gallo *et al.* 2011). Coupling an increase in feed rate with an increase in atomizing gas flow is suggested to avoid further challenges (Cheow *et al.* 2010; Gallo *et al.* 2011) and to increase yield (Tajber *et al.* 2009b). The increase in drying time due to the increased moisture (Maltesen *et al.* 2008) could possibly prolong crystallization time in spray drying (Chan and Chew 2003) and increase the formation of hydrates (Chidavaenzi *et al.* 1997). The dependency of crystallinity on feed rate is claimed insignificant by Das et al. (2010), although opposing results are also available (Islam and Langrish 2009). There are studies where the effects of feed rate are found not to be significant for product characteristics (Bosquillon *et al.* 2001; Maltesen *et al.* 2008).

The physical attributes like hose material and length may contribute to the quality if they subject the liquid mixture to energy changes (light, temperature, radiation) or unsuitable materials. Temperature oscillation is known to promote crystallization (Stieger and Liebenberg, 2012). Crystallization can also be promoted in capillary tubes that affect evaporation, turbulence and convection, such as feeding hoses. These types of factors are considered meaningful mainly for supersaturated solutions.

## 4.3 Spraying phase

In the spray phase the produced feedstock is broken up into a spray of spherical droplets sized 5-600 μm (i.e. atomization) by using different techniques (Masters 2002). The size of the droplets is not the same as particle size but they are closely related. This is due to the droplet drying. Spray is produced due to the frictional forces created between the atomizing gas and the liquid feed. This process can be divided in two phases: tearing of liquid into thin filaments and further disintegration of droplets (Hede *et al.* 2008). Thereafter the produced droplet leaves the atomizer and gets into complex interaction with the surrounding gas, with other droplets in the spray cloud and with the unknown stresses within the droplet. There are different theories and neither of them is considered accurate due to the complexity of the process. The main adjustable parameters in spraying phase are: the nozzle, the liquid feed and the spraying gas.

The properties of the liquid feed that affect the performance of the pneumatic nozzle are surface tension, density and viscosity of the liquid (Masters 2002, Hede *et al.* 2008) of which the viscosity is said to be the most important parameter in controlling the mean droplet size (Hede *et al.* 2008). The surface tension and viscosity are considered to be opposing forces for the disintegration of the liquid (Masters 2002) whereas the effects of density are rather complex (Hede *et al.* 2008). An increase in feed rate, viscosity (Masters 2002; Gallo *et al.* 2011) and surface tension tend to produce larger droplets (Gallo *et al.* 2011). The dependency of droplet and particle size was verified by Kawakami *et al.* (2010). Larger droplets are more favorable for crystallization because of the longer lifetime of the droplets and hence higher chances of crystallization (Elversson and Millqvist-Fureby 2005a).

Pneumatic nozzle turn-down ratio and capacity are somewhat more limited than for example in the rotary atomizer and that is why duplication of the nozzles is used to increase the feed rate. The advantages of pneumatic nozzle are the high homogeneous spray quality and small mean droplet size and considerably low operating pressures (Masters 2002). The mean droplet size can reach 2-5 μm with small nozzle bodies, low feed rates and low viscosity feedstocks. The operational pressures of pneumatic nozzles are typically below 7 bars whereas in pressure atomization the pressures used can be more than 500 bars. There are four different types of pneumatic nozzles: internal mixing two fluid nozzle, external mixing two fluid nozzle, combined internal-external mixing three fluid nozzle and pneumatic cup atomizer nozzle.

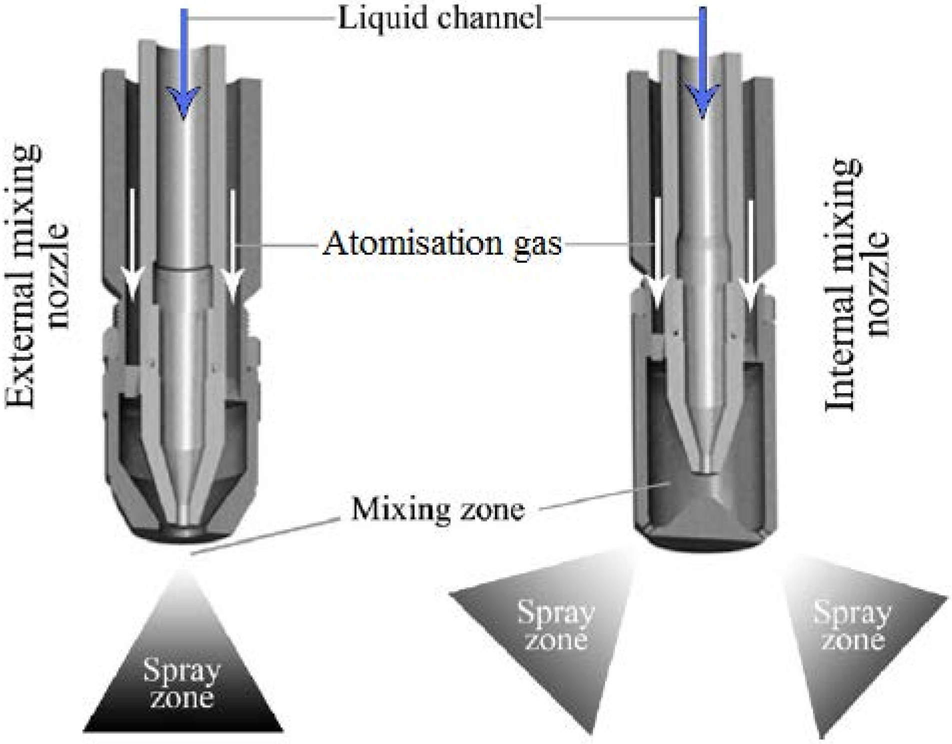


Figure 12. Examples of external (left) and internal (right) mixing nozzle designs (Salman *et al.* 2007 in Hede *et al.* 2008, modified from the original)

The internal mixing nozzle contacts the air and liquid within the nozzle head whereas the external type contacts them outside the nozzle head (Masters 2002) (Fig. 12). Due to these structural differences the internal mixing achieves higher energy transfer and the external mixing provides greater control on the gas and the liquid streams. The combined internal-external mixing nozzle combines these two benefits and is therefore often used for difficult high viscosity liquids and also to produce aerosol size range products. The pneumatic cup atomizer contacts gas and liquid at the rim of a rotating nozzle head. It is used to produce fine sprays from low and medium viscosity feeds. There are also many variations of the four nozzle types (Hino *et al.* 2000; Ozeki *et al.* 2006). The most commonly used design is the external mixing two-fluid type of nozzle (Hede *et al.* 2008) which was also used in this study. In this type of a nozzle the atomizing gas and the liquid feed go separate ways to the nozzle and collide just outside the nozzle tip to produce a spray cone (Masters 1991). The colliding outside the nozzle tip does apparently not mix the liquid feed significantly (Janssens et al. 2009) unless two different feed passages are used (Ozeki *et al.* 2006). Spray cones are dictated by the properties of the liquid, the nozzle design and operating parameters and affect the product quality (Masters 2002).

The nozzle orifice in pneumatic nozzles is larger than in a pressure nozzle which is an advantage due to the smaller likelihood for nozzle clogging (Masters 2002). There are various designs for spray orifice shape that produce different kinds of spray cones such as a full cone, a hollow cone and a flat cone (Hede *et al.* 2008). An increase in the nozzle orifice size has been noted to increase the crystallinity of the product (Alves and Santana 2004), an increase in the particle size (Elversson *et al.* 2003) and an increase in wall deposition due to the increase in spray cone breadth. The use of suspensions with high solid content may subject it to a milling effect in the spray nozzle (Chidavaenzi *et al.* 1997) and this milling effect could increase the apparent solubility that could potentially increase the amorphous content (Buckton and Beezer 1992 in Chidavaenzi *et al.* 1997). The solubility of the solids in the solution would be further influenced by the temperature of the nozzle as it passes by. To minimize this influence of temperature some nozzle models can be cooled with a water circulation system.

The quality and amount of the spraying gas has effects on the product quality. An increase in the spraying gas density while maintaining the velocity increases the dynamic force of the gas and results in a decrease in mean droplet size (Masters 1991). The use of different spraying gases may affect the morphology of the particles (Islam and Langrish 2010b). The amount of sprayed gas can be regulated by adjusting the pressurized gas flow rate by a control valve (Masters 2002). Therein the spraying gas amount can be adjusted by adjusting the pressure or the airflow.  The spraying gas pressure is said to have a minor impact on the product quality (Bosquillon *et al.* 2001). This can be considered as an interesting result because the effect of the gas flow was considered as the factor with the most significant effect on particle size by Maltesen *et al.* (2008). An increase in gas flow increases yield (Goula *et al.* 2005; Amaro *et al.* 2011), decreases geometric particle size (Juslin *et al.* 1995; Elversson *et al.* 2003; Goula *et al.* 2005; Cheow *et al.* 2010; Amaro *et al.* 2011; Gallo *et al.* 2011) and specific surface area (SSA) (Amaro *et al.* 2011) but is said to be insignificant in relation to the level of crystallinity in the product (Das *et al.* 2010). The air-to-liquid mass flow rate (ALR) is found to be more useful than the gas flow itself (Hede *et al.* 2008; Cheow *et al.* 2010; Gallo *et al.* 2011).

## 4.4 Drying phase

The produced spray of spherical droplets is contacted with gas involving flow and mixing. This causes the droplets to dry into individual particles while moving in a gaseous drying medium (Masters 2002). The heat of evaporation for a droplet drying is supplied by the heat of the drying medium, which is usually air or an inert gas like nitrogen (Maltesen *et al.* 2008; Masters 2002). The details in the drying phase are considered rather challenging to describe due to the experimental challenges with nucleation and crystal growth and theoretical challenges with material properties in supersaturated solutions (Vehring *et al.* 2007).

Two types of moisture can be found in the liquid feed: bound and unbound moisture (Masters 2002). Bound moisture can be found from capillaries in solids, adsorbed in solid surfaces, from cells, fiber walls or in crystals as hydrate. The rest of the moisture in a hygroscopic material is unbound moisture. In a non-hygroscopic feed all moisture is unbound. The amount and quality of the moisture in a material is a parameter that defines the drying characteristics for a droplet. The drying can be divided into two steps: constant rate drying from the surface and drying after the surface saturation can no longer be maintained. In the first drying step the temperature remains constant due to the evaporation and product is not subjected to any rapid temperature increase. In the second step the particle temperature could rise, but it is subjected to lower temperatures. The rate of the water evaporation is found to affect the surface morphology greatly (Shi *et al.* 2012).

The drying process of solution and emulsion differ from the suspension (Fig. 13). A suspension droplet, when contacted with drying air, begins to dry more or less at a constant rate (Masters 2002). This brings the insoluble particles closer to each other. The next drying phase begins when the surface wetness can no longer be maintained due to the insufficient capillary mechanisms. This is the beginning of the funicular phase where the liquid is in pores filled with capillary flow. The final state of drying starts when capillary flow ceases and vapour diffusion starts to dominate. This pendular state continues until the particle has dried. The drying of a solution or emulsion droplet starts also more or less at a constant rate when contacted with drying air. In this period the temperature of the droplet can be equated to that of the saturated solution but the surface concentration can be less than equal with saturated solution. This period of drying ceases when the droplet moisture content falls to a critical value and a solid phase forming at the droplet surface is detectable. The increased solidification decreases the moisture migration from the core and heat transfer starts to exceed mass transfer. This causes the particle to heat up and if the surrounding air temperature is adequately high (above the boiling point of the droplet solution) the liquid inside the droplet starts to form vapour. The vapours will escape the particle via the surface and may affect the morphology depending on the nature of the solid layer on the droplet surface. If the solid layer is easily penetrated e.g. a porous surface, the morphology is less affected. On the other hand, if the surface is non-porous `plastic´ (impervious) film, the evaporation time for removal of complete volatiles is greatly extended and the droplet may be subjected to significant morphology modifications, such as expanding, collapse, rupture or even disintegration. The thickness of the solid layer increases as the solid concentration of the feed increases (Elversson *et al.* 2003; Fu *et al.* 2012). In a co-current mode spray drying the droplets does not usually reach boiling point level moistures. Irrespectively of the conditions used the volatiles movement within a spray dried droplet is first controlled by liquid diffusional mechanisms and then by vapour diffusional mechanisms.

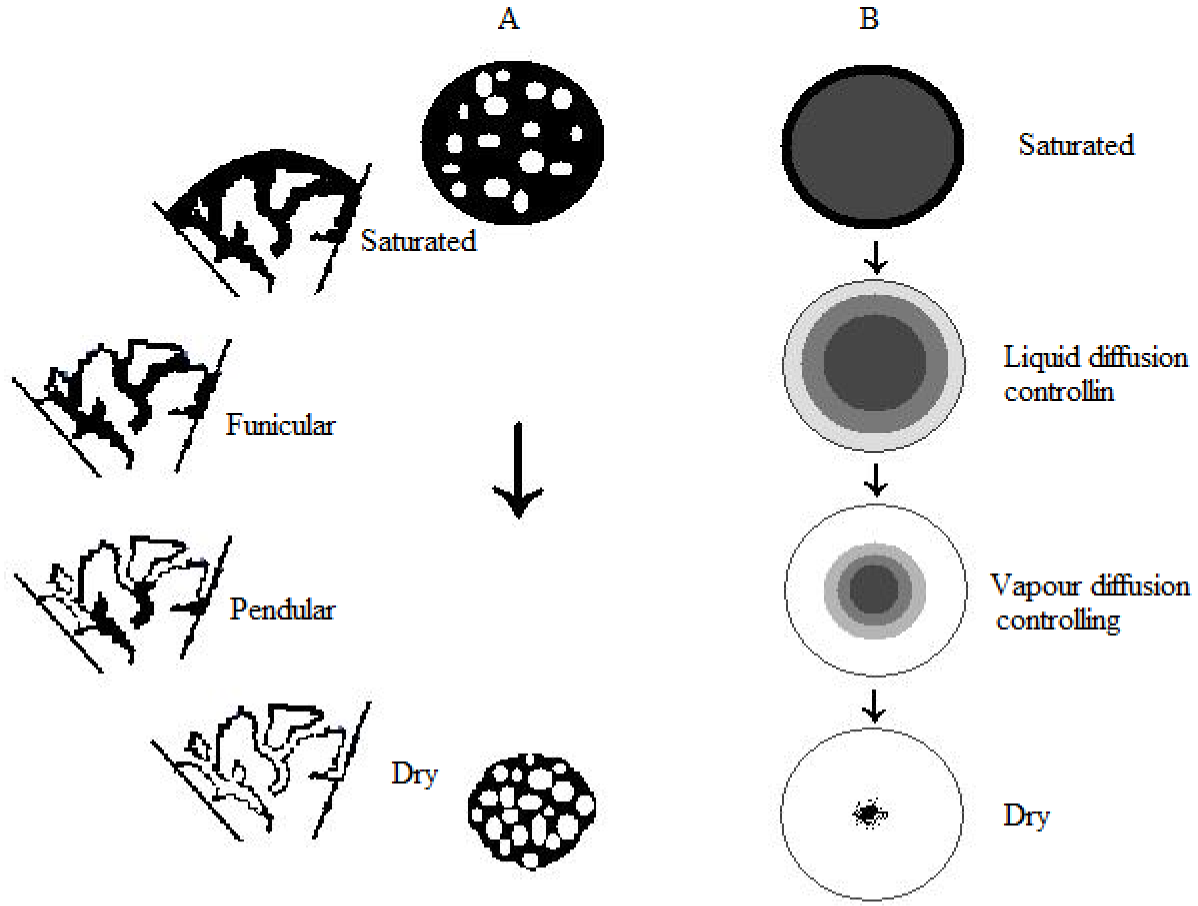


Figure 13. The drying phases of suspension (A) and solution/emulsion (B) (based on Masters 2002).

During spray drying process the initially spherical droplets undergo both size and shape changes (Masters 2002). Some may expand, others collapse, form blow holes, agglomerate or disintegrate on mechanical handling. The resulting material will be powder, granules or agglomerates depending upon the physical and chemical properties of the feed, the dryer design and parameters used. It may also have a wide degree of different particle shapes because of the individual conditions for each particle. The rapid solidification in spray drying may cause phase separation or crystallization that can be harmful for the protein structure (Ståhl *et al.* 2002). There apparently is a critical crystallization period in the drying phase, which dependent on moisture and temperature (Woo *et al.* 2012). Modifying this period would possibly affect the crystallinity of the product. This possibility for crystallization is criticized by Chidavaenzi *et al.* (1997) due to the lack of time for crystallization.

An increase in the inlet temperature in spray drying was found to increase density (Bosquillon *et al.* 2001), the level of crystallization (Chiou *et al.* 2008; Islam and Langrish 2009; Mezzena *et al.* 2009; Islam and Langrish 2010a; Fu *et al.* 2012), yield (Goula and Adamopoulos 2005), outlet temperature (Gallo *et al.* 2011), evaporation rate (Shi *et al.* 2012), variation of size (Fang *et al.* 2012), particle size (Fu *et al.* 2013) and produce particles with increased surface roughness (Maas *et al.* 2011; Fang *et al.* 2012). The particle size was found to be relatively unaffected by temperature (Maas *et al.* 2011). Combining high inlet temperatures with low feed rates are found to produce smaller, denser and more homogenous particles (Cabral-Marques and Almeida 2009).

The effect of inlet temperature is claimed to be related to the glass transition temperature ($T_g$) of the material (Islam and Langrish 2009) (Fig. 14). It was observed that with low temperatures the yield was decent, when the presence of moisture decreased the $T_g$ (Islam and Langrish 2009, Shi *et al.* 2012). When the inlet temperature was increased, the particle temperature $T_p$ was increased, the moisture content decreased and allowed the $T_g$ to increase resulting in a decrease in yield due to ´The Stickiness Barrier´ that was reached. In this temperature area an amorphous product is produced that behaves in a sticky manner in a spray dryer. However, increasing the temperature even further results in an increase in particle temperature $T_p$, but as the materials $T_g$ is reached the difference in ($T_p$ -$T_g$) increases resulting increased yield and crystallinity. This is further confirmed by Islam et al. (2010) by insulating the system to produce higher $T_p$ and by increasing the humidity of the drying gas to lower the $T_g$. The material produced with this installation was significantly crystalline. The increase in crystallinity is postulated to increase in larger scale equipments that have longer residence times and hence more time for crystallization (Islam and Langrish 2009). This hypothesis was later challenged by Das *et al.* (2010) as they noted that the highest temperatures do not necessarily produce the most crystalline products in a pilot-scale spray dryer. The reason was thought to be caused by the slower drying of larger particles that did not produce adequate difference in ($T_p$-$T_g$) in these temperatures and timescales.

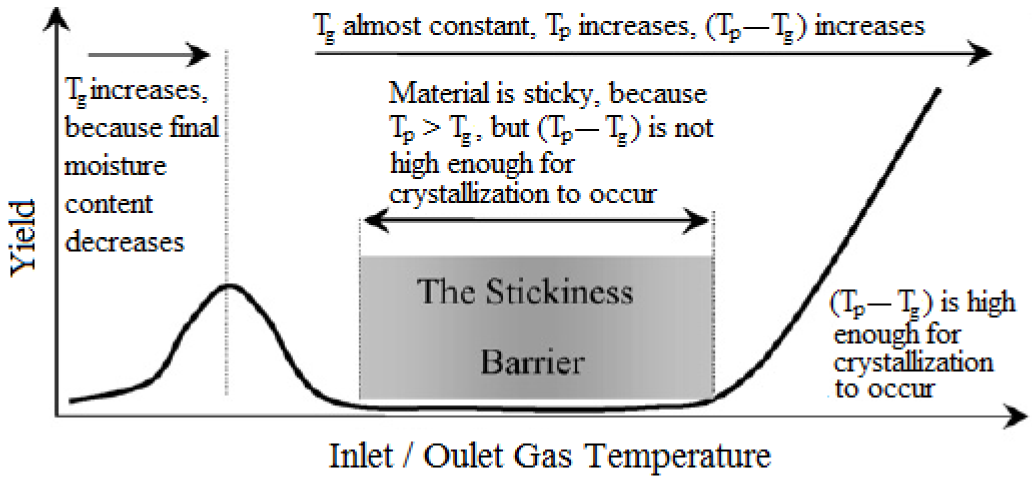


Figure 14. The concept of stickiness barrier represented in schematic picture (Islam and Langrish 2009, modified from the original)

Although thermal stress can be an issue for thermolabile substances such as proteins (Maa *et al.* 1998; Millqvist-Fureby *et al.* 1999; Ståhl *et al.* 2002) and certain salts (Gad *et al.* 2012) it is considered as a minor problem in spray drying. The outlet temperature is considered as a limiting factor by Ståhl *et al.* (2002). The droplets are only briefly exposed to the inlet temperature (Masters 1991) and the product temperature will remain considerably lower than the inlet temperature due to the cooling by latent heat vaporization (Chan and Chew 2003). The temperature can be also reduced by lowering the feed temperature compared to the drying gas temperature (so called “wet bulb” effect).

The drying gas quality, content and flow rate have significant effects on the drying performance of spray dryer. Most often the drying medium is atmospheric air, but nitrogen and carbon dioxide have been widely used as well. The used gas type may have an effect on the solid state properties (Islam and Langrish 2010b; Bianco *et al.* 2012) and morphology of the spray dried powders (Nolan *et al.* 2009; Islam and Langrish 2010b). This may be partly due to the different humidities present in the gases and partly due to the different physical properties of the gases. In a closed loop system there is also a theoretical possibility that the recirculated gas can remain contaminated despite the condensation phase and affect the product properties (Bianco *et al.* 2012). The used drying gas can be humidified (Islam *et al.* 2010) or dried (Masters 2002; Goula and Adamopoulos 2005; Maltesen *et al.* 2008) before contacting with the liquid feed. The lower humidity of the drying air combined with lower inlet temperature can improve product yield (Goula and Adamopoulos 2005).

The drying chamber is usually a cone-shaped structure made of stainless steel (glass in laboratory) (Weiler *et al.* 2010) varying in size and form according to the flow mode and operation parameters used (Masters 2002). Modifying the drying chamber (Maury *et al.* 2005) or adding insulation (Masters 2002; Islam and Langrish 2010a; Islam *et al.* 2010) can increase the thermal efficiency of the system and crystallization (Islam and Langrish 2010a) via increase in outlet temperature. Modifying the drying chamber dimensions is also a factor that affects the residence time for the particle in the system (Chan and Chew 2003). An increase in the dimensions is postulated to increase the level of crystallization (Islam and Langrish 2010a).

The gas and droplet flow inside the drying chamber can either be to the same direction (co-current flow mode), in the opposite direction (counter-current flow mode) or a mixture thereof (Masters 2002). The co-current flow mode is a rapid process and suitable for sensitive products because it does not subject the product to any rapid temperature increases. The counter-current flow mode instead, subjects the driest powder to the most intense heat and also to the newly formed droplets. The latter mode is suited for coarse droplet size nozzle atomization to allow larger particles to dry more efficiently. Mixed-flow mode can be used to produce small particles but it subjects the particles to higher temperatures during the process. Decreasing the temperature gradient around the atomizer will decrease the evaporation rate (Ståhl *et al.* 2002). This will lead to more uniform size and shape of the particles. This will also increase particle density and roundness.

The spray drying can also be done in lower or higher pressures than atmospheric pressure (Masters 2002). Lower pressure conditions increase the rate of solvent evaporation (Masters 2002; Stieger and Liebenberg, 2012) and high pressure has been used only recently to encourage denser packing structure but may also impede crystallization (Masters 2002).

Pressure change also changes the solubility of a given polymorph or solvate possibly even at the expense of another (Stieger and Liebenberg, 2012). This might encourage recrystallization on certain occasions. There is also some evidence that pressure can induce changes in the solid form. Pressure can also induce structural changes in solid-state molecular crystals, though this is thought to be only a partial change. It was found that lowering the pressure in spray drying process increases the level of crystallinity (Eslamian and Ashgriz 2006). The usages of systems with other than atmospheric pressure are in most cases found technically and operationally challenging (Masters 2002).

### 4.5 Recovering phase

After the drying chamber the discharge of the particles takes place at the base of the drying chamber and in a dry collection equipment e.g. cyclone, bag filter or electrostatic precipitator (Masters 2002). It can also be recovered wet in wet scrubbers and wet cyclones. The product, when recovered dry, can be mixed with the main powder fraction leaving the base of the drying chamber or reprocessed in the feed formulation or transported for further processing. Further processing can be a cooler, an agglomerator or a granulator. The wet recovery systems are considered to be insufficiently hygienic for most dairy products, food products and pharmaceuticals if the solids need to be recovered as powders.

The cyclone is a dry centrifugal particle separator used in conjunction with a spray drying chamber (Masters 2002). In a cyclone the gas and particles form a vortex where the particles are subjected to centrifugal forces and drag forces of the air. Powders and air swirl down the cyclone, where the powder leaves the cyclone and deposit into the product vessel while the air spirals upwards along the axis of the cyclone exiting from the top (Fig. 15). The deposition place for a particle is dependent on the drying characteristics of the product, structure of the drying chamber, speed of spraying and drying gases. Cyclones are low in costs and easy for maintenance, though they are not 100% efficient and therefore require some additional secondary collector stage. The efficiency of a standard cyclone (height 0.340 m and diameter 0.135 m) is said to be poor for smaller particle sizes (Mosén *et al.* 2004; Maltesen *et al.* 2008). The cut-off diameter (less than 50% of particles captured) for this cyclone is considered to be 2 μm (Mosén *et al.* 2004). Changing the drying gas velocity and cyclone diameter might increase efficiency. A smaller cyclone is found to increase yield and preserve enzymatic activity better than a larger one (Bögelein and Lee 2010). This is thought to be because of the better retention and separation of FPF in the cyclone. A cyclone can operate under pressure or in vacuum (Masters 2002). An increase in aspirator value can increase the efficiency in cyclones particle separation (Buchi process parameters guide 2012) and a decrease in product cohesiveness (Boraey *et al.* 2012)

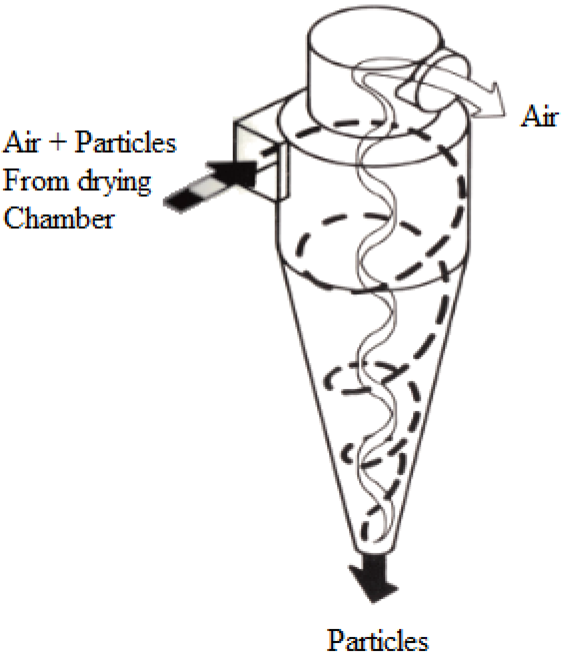


Figure 15. Cyclone separation principle (Masters 2002, modified from the original)

The secondary collector stage collects the finest fraction simultaneously purifying the exhausting gas with dry or wet based mechanism (Masters 2002). A bag filter is one of the most commonly used devices for secondary collector stage and it may be used occasionally even to replace the cyclone. It is considered as virtually 100% efficient. An electrostatic precipitator is sometimes used to replace a cyclone and bag filter combination, although it is rather expensive. It is advisable to consider the nature of the product while choosing the collection equipments, because it may subject the particles to some mechanical forces and alter the product size and shape. Cyclones, for example, tend to increase the fine particle size especially for fragile particles.

The amount of yield is a result of many variables and their interactions. Feed concentration (Maltesen *et al.* 2008; Amaro *et al.* 2011), feed rate (Amaro *et al.* 2011), and inlet temperature are found to be parameters that have positive effect on the yield when increased. Small particle size is found to decrease yield (Mosén *et al.* 2004; Maltesen *et al.* 2008). Spray gas flow had a negative correlation with yield when increased. Combining the increase of feed concentration with either spray gas flow decrease or feed concentration increase resulted in significant effects.

## 4.6 The spray drying parameters

The spray drying parameters from the literature are summarized and explained in Table 1. As can be observed the effect of many parameters seem to be quite varying. This indicates possibly the complexity of the spray drying process, the dependency of parameters from the quality of the substance and also the used range of the parameters. For each row two references are specified.

Table 1. Spray drying parameters and their effects

| Parameter<br>Dependence | Aspirator | Humidity drying gas | Drying gas type | Inlet Temperature | Spray gas flow | Feedrate | Solids concentration | Organic solvent instead of water | solids composition | Closed or open SD cycle | Nozzle diameter | Sources |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outlet temperature | ++ |  |  | +++ | + | ++ |  |  | + |  |  | 1 |
| Particle size |  |  |  |  | ++ | + | ++0 | 0+ |  |  | + | 2 |
| Humidity in product |  |  |  | ++ |  |  |  |  |  |  |  | 3 |
| Yield | + | + |  | + | ++ | + | ++ | + | + |  |  | 4 |
| Crystallinity |  | + | ++ | ++ |  | + | +0 | ++ | ++ | ++ | + | 5 |
| compactibility |  |  |  |  |  |  | + |  | + |  |  | 6 |
| flowability |  |  |  |  | + |  | + |  | + |  |  | 7 |
| Carrs indice |  |  |  |  |  |  | + |  | + |  |  | 8 |
| Respirable fraction |  |  |  |  |  | + | +++ |  | + |  |  | 9 |
| Density |  |  |  | + |  |  | ++ | ++ | ++ |  |  | 10 |
| Morphology |  |  | ++ | ++ |  | ++ | ++ | ++ | ++ | ++ |  | 11 |
| Particle size Distrib. |  |  |  | + |  |  | + | + |  |  |  | 12 |

|  |  |  |  |
|---|---|---|---|
| 1 | Beck-Broichitter et al. 2012, Gallo et al. 2011 | 0 | no influence |
| 2 | Mosen et al. 2004, Tajber et al. 2009 | + | minor influence |
| 3 | Maltesen et al. 2008, Shi et al. 2012 | ++ | considerable influence |
| 4 | Sansone et al. 2009, Boraey et al. 2012 | +++ | major influence |
| 5 | Bianco et al. 2012, Mezzena et al. 2009 |  |  |
| 6 | Gallo et al. 2011, Gonissen et al. 2007 | 🟩 | increasing parameter |
| 7 | Gallo et al. 2011, Gonissen et al. 2007 | 🟦 | decreasing variable |
| 8 | Tajber et al. 2009, Gallo et al. 2011 | 🟥 | increasing variable |
| 9 | Traini et al. 2012, Adi et al. 2008 |  |  |
| 10 | Maltesen et al. 2008, Nolan et al. 2011 |  |  |
| 11 | Islam and Langrish 2010b, Harjunen et al. 2002a |  |  |
| 12 | Nolan et al. 2011, Fang et al. 2012 |  |  |

# 5 ANNEALING

The inherent instability of many water soluble amorphous substances results possibly in uncontrolled crystallization when exposed to high humidities (Elamin *et al.* 1995) and inadequately high temperatures (Burnett *et al.* 2004). To address this instability a process that will increase the stability is necessarily. One way to solve this problem is to expose the instable amorphous material to conditions that would allow the material to crystallize in a controlled environment and in short time frames (Brodka-Pfeiffer *et al.* 2003). This process where temperature and humidity are controlled is referred as annealing but is known also as conditioning.

Model substance will be annealed in order to study their solid state transformation tendencies and therein their storage stabilities (Brodka-Pfeiffer *et al.* 2003). This process is done to the raw materials as well as for the spray dried products. The annealing of the raw materials was designed to address the concern that the micronized raw material might not be totally crystalline (Fix and Steffens 2004; Grisedale *et al.* 2011). An increase in amorphous character has been observed when micronizing material with ball milling (Willart et al. 2004).

The annealing solvents used were ethanol and water. They acted as plastizers to promote the molecular movement needed for solid state transformations (Ahlneck and Zografi 1990). A more water soluble substance would be annealed with water vapour (Ali *et al* 2012) although ethanol vapour could possibly have been equally adequate (Trofast *et al.* 1992). A less water soluble substance would be annealed with ethanol vapour which could facilitate its crystallization better than water or water-ethanol solutions (Ahmed *et al.* 1996). The annealing values chosen (temperature and solvent vapour activity) should exceed certain levels in order for the process to happen (Brodka-Pfeiffer *et al.* 2003; Adilovic 2012; Grisedale *et al.* 2012). It is also advisable to minimize locally progressive crystallization of powder (Buckton and Darcy 1995) and add a purging gas to facilitate mixing (Trofast *et al.* 1992). Further optimization is suggested to minimize unwanted particle growth which seemed to increase with the used relative humidity (Brodka-Pfeiffer *et al.* 2003).

The crude powder annealing method is conducted by subjecting the sample for the chosen solvent vapours in a tightly sealed box. This box would be a two storied transparent box kept in room temperature (23$^{o}$C) with a sealable door. In the water vapour annealing system a salt solution of NaBr in water is put in petri dish on the lower floor to provide the desired relative humidity. In the ethanol vapour annealing system the boxes have ethanol activities that were also created on a petri dish with the help of salt solutions. The annealed substance would be located on the higher floor spread into a petri dish or applied on an XRPD plate. After the crude tests, a more elaborate small scale flow-annealing system (Fluxus, AstraZeneca, Sweden) is used to anneal the more water soluble substance. This equipment is developed by AstraZeneca (Trofast *et al.*, 1992) and is described in an MSc thesis by Adilovic (2012).

# 6 AIMS OF THE STUDY

The aim of this study was to obtain basic knowledge of the applicability of a spray dryer for inhalation particle production and its process parameters effects on particles physicochemical properties. From the many process parameters the concentration of the solid substances, inlet temperature and concentration of organic solvent were chosen as variables due to their apparent effects on product quality and especially on solid state. The greater goal was to provide some information about the crystallization tendency of solutes related to chosen process variables. The possibility to anneal the particles was also studied.

# 7 MATERIALS AND METHODS

## 7.1 Materials

Salbutamol sulphate (Fig. 16) is white crystalline powder that is freely soluble in water and very slightly soluble in ethanol (Sweetman 2009). However, it is not hygroscopic and therefore will not form hydrates (Columbano *et al.* 2002). Solubility in various ethanol / water mixtures decreases almost linearly with the increase of ethanol concentration, reaching its lowest value in pure ethanol (Ali *et al.* 2012). This is in accordance with the observed solubility pattern of most salts in ethanol / water mixtures. There are at least two polymorphic forms for salbutamol sulphate (Palacio *et al.* 2007). One polymorph (referred to as type I) is obtained when crystallized from water and another (referred to as type II) by resolving a methanol crystallized material in methanol and drying it as a suspension in vacuum. The extensive use of the racemic salbutamol sulphate as a bronchodilator is somewhat questionable considering the fact that the biological effects of different isomers differ considerably (Page and Morley 1997).

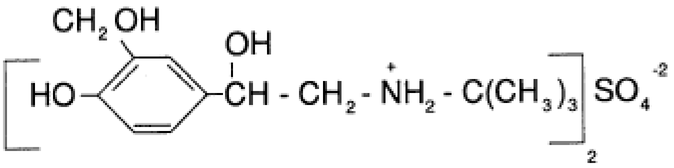


Figure 16. Molecular structure of salbutamol sulphate (Ward and Schultz 1995), modified from the original.

Budesonide (AstraZeneca) (Fig. 17) is white crystalline powder that is practically insoluble in water and sparingly soluble in ethanol (Sweetman 2009). It follows the solubility pattern of a weak electrolyte or non-electrolyte and is more soluble in ethanol than water, reaching highest solubility around 90% ethanol solutions (Ali *et al.* 2010). Currently there are no known polymorphs for budesonide (Velaga *et al.* 2002; Steckel *et al.* 2004; Kubavat *et al.* 2012) but different crystalline habits have been produced with different cohesive-adhesive balance (CAB) and mechanical properties (Kubavat *et al.* 2012).

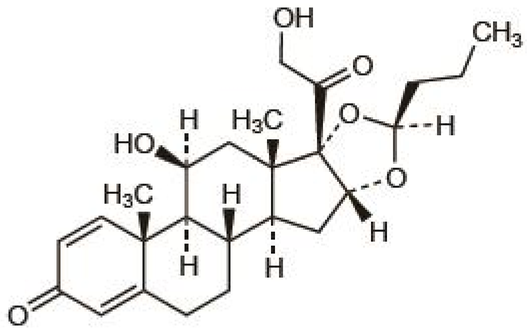


Figure 17. Molecular structure of budesonide (Sweetman *et al.* 2009), modified from the original.

Micronized salbutamol sulphate was obtained from Letco Meridian Pharmaceuticals, whereas micronized and unmicronized budesonide were provided by AstraZeneca DPS (Sweden). Solvents used were: ethanol purchased from Kemetyl (Sweden) and, deionized water obtained from Millipore (EMD Millipore Corporation, Billerica, MA, USA) water purification system.

## 7.2 Design of experiments

### 7.2.2 General design

Spray drying is a complex process and there are many factors that can affect the quality of the product. There are seven process parameters that are specified by the spray dryer manufacturer (Büchi 2012):

1. Aspirator
2. The humidity of the drying gas
3. Inlet temperature
4. Spray gas flow speed
5. Feed rate
6. Concentration of solids
7. Solvent

From these parameters concentration of solids (6.), inlet temperature (3.) and concentration of organic solvent (7.) were chosen as variables for the conducted experiments.

Concentration of solids was chosen as a variable for its effects on solid state (Chidavaenzi *et al.* 1997; Alves and Santana 2004; Bianco *et al.* 2012; Stieger and Liebenberg 2012), particle size, yield and morphology (Maltesen *et al.* 2008; Cheow *et al.* 2010; Amaro *et al.* 2011). The chosen values were relative values in the current solvent mixture in order to maintain similar saturation levels and therein similar crystallization tendencies (Stieger and Liebenberg 2012).

Inlet temperature was chosen as a variable for its effect on solid state (Alves and Santana 2004; Chiou *et al.* 2008; Das *et al.* 2010; Islam and Langrish 2009; Mezzena *et al.* 2009) and humidity (Burnett *et al.* 2004). The chosen inlet temperature range was chosen on the basis of the glass transition temperatures ($T_g$:s) and the limitations of the used system. This decision was based on the suggestion that the crystallization rate would be dependent on the relation between the glass transition temperature and the material temperature (Islam and Langrish 2009). Variation in inlet temperature has also been indicated to contribute to drying efficiency (Masters 2002; Alves and Santana 2004).

Concentration of organic solvents was chosen as a variable because of its effects on solid state (Harjunen *et al.* 2002; Gad *et al.* 2011; Gilani *et al.* 2005), particle size (Elverssons and Millqvist-Fureby 2005a; Bürki *et al.* 2011) and particle shape (Gad *et al.* 2011; Kaialy *et al.* 2010). The chosen organic solvent was ethanol which, in addition to other effects, has been found to improve dispersion properties of the spray dried powder (Gilani *et al.* 2005). The chosen ethanol concentrations in relation to water content were chosen to range from nearly equal ratio to higher ethanol concentrations. The width of the range was designed to be a bit larger than in Bürki *et al.* (2011) to allow larger visibility for the differences in process and in product quality. The ethanol concentrations used were limited by the solubility data of salbutamol sulphate (Ali *et al.*2012) and budesonide (Ali *et al.*2010).

The values chosen for the experiments in DOE1 are listed in the Table 2. Air pressure and movement in the spray drier is a sum of two components: aspirator value and rotameter value. Aspirator provides the air movement for the system and the rotameter is a regulating system for the spray gas flow. The aspirator value was chosen to be kept at maximum value (100%) in order to provide efficient drying and separation in cyclone (Büchi 2012). The value for the rotameter was chosen to represent a rough median of the values used in similar studies (Buttini *et al.* 2008a; Mezzena *et al.* 2009; Nolan *et al.* 2009; Tajber *et al.* 2009a).

Table 2. The values and value ranges used in the DOE1 experiments.

| | | Budesonide | Salbutamol |
|---|---|---|---|
| 1. | Aspirator (%) | 100 | 100 |
| 2. | Humidity drying gas | ND | ND |
| 3. | Inlet temperature ($^{o}$C) | 80-140 | 80-100 |
| 4. | Spray gas flow (rotameter value) | 40 | 40 |
| 5. | Feed rate (%) | 17 | 17 |
| 6. | Solids concentration (% of saturation) | 50-100 | 50-100 |
| 7. | Organic solvent concentration (%) | 50-99.5 | 40-90 |

The humidity of the drying nitrogen was not confirmed but it was assumed to be dry (Table 2). The Inlet temperature range was designed so that the outlet temperature range would get values from below the $T_g$ of salbutamol sulphate (66.7$^{o}$C, Grisedale *et al.* 2011) all the way over the $T_g$ of budesonide (92$^{o}$C, Nolan *et al.* 2009). However, due to the early learning phase it was thought that the low boiling point of ethanol (78$^{o}$C Sweetman 2009) would potentially limit the inlet temperature range for safety reasons. This assumption had probably little effect on the salbutamol sulphate (low $T_g$ value) and it was later corrected for the budesonide assay. The higher concentration (100% saturation, Table 2) was achieved by mixing the solvent mixture with excess solids overnight. This mixture was then filtered and spray dried or filtered and diluted to produce less saturated solutions. The used feed rate was chosen on the basis of other similar studies (Buttini *et al.* 2008a; Mezzena *et al.* 2009; Nolan *et al.* 2009; Tajber *et al.* 2009a).

On the basis of the presented variable choices a factorial design model with the chosen three variables (inlet temperature, solids concentration and ethanol concentration) was created. The design work was partly done with Modde- software (Umemetrics Academy, 2002). With the Modde software the experiments were divided into fractional factorial designs and one these was chosen for both test substances. The final chosen fractional factorial design is presented in Figure 18.

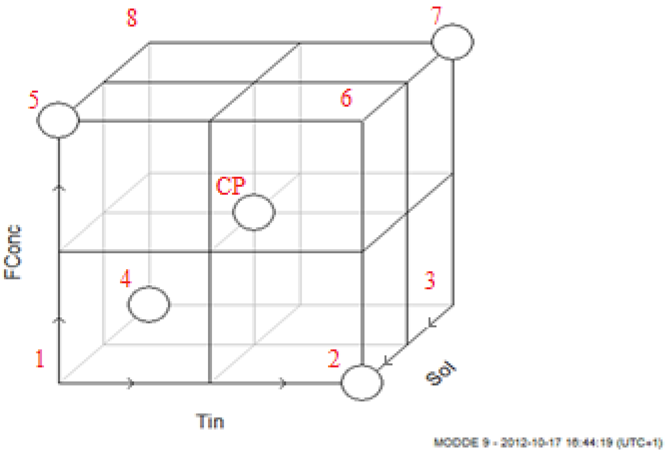


Figure 18. The fractional factorial design. The circled points were chosen to be tested by the MODDE 9 -program.

### 7.2.3 Salbutamol sulphate DOE

The DOE1 for salbutamol sulphate was done according to the following fractional factorial design (Fig. 18). The measured points are listed in Table 3. The used starting material for DOE1 points (Table 3) was micronized and verified to be crystalline by PXRD and sized 1.6 μm by laser diffraction.

Table 3. Salbutamol sulphate DOE1 points

| | CP 1 | Point2 | Point4 | Point5 | Point7 | Point4b |
|---|---|---|---|---|---|---|
| Ethanol (%) | 70 | 40 | 40 | 90 | 90 | 40 |
| Salbutamol (%) | 4 | 15 | 7 | 0.2 | - | 7 |
| Tinlet ($^oC$) | 91 | 100 | 81 | 80 | 100 | 81 |
| Tout ($^oC$) | 52 | 59 | 45 | 54 | - | 44 |
| feed speed (%) | 17 | 17 | 17 | 17 | 17 | 17 |
| rotameter value (spray air flow) | 40 | 40 | 40 | 40 | 40 | 40 |

The results from DOE1 were all XRPD amorphous and therefore three further studies were designed to increase or clarify the effects of different parameters on crystallinity. First two of the studies focused on the effects of the solid concentration in the liquid feedstock (Study I, II, table 4) and the third one (Study III, table 4) focused on the effect of temperature. Study I was designed to study the different performances of a saturated solution (batch 1, table 4) and a suspension that had 10% extra solids (batch 2, table 4) compared to the former one. These values were calculated from the studies presented by Ali *et al.* (2012). Study II was designed to study the different performances of 110% (batch 3, table 4) and 120% suspensions (batch 4, table 4).

Table 4. The further studies for sabutamol sulphate

| | Study I | | Study II | | Study III | | |
|---|---|---|---|---|---|---|---|
| Batch Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Ethanol (%) | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Salbutamol (%) | 16 | 17.5 | 15.1 | 17.4 | 12.5 | 12.4 | 13 |
| Tinlet ($^o$C) | 101 | 101 | 101 | 101 | 80 | 101 | 141 |
| Tout ($^o$C) | 59 | 61 | 61 | 57 | 48 | 57 | 80 |
| feed speed (%) | 17 | 17 | 17 | 17 | 17 | 17 | 17 |
| rotameter value (spray air flow) | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Nozzle cooling ($^o$C) | - | - | 15.1 | 15.1 | 15.1 | 15.1 | 15.1 |

For Study II an extra element, namely a nozzle cooling system, was introduced to the original hardware. Nozzle cooling systems prevents the drying gas induced nozzle heating that might affect the solubility of the solute. The nozzle cooling system was introduced because the results obtained by Chidavaenzi *et al.* (1997) had suggested the use in order to further assess the results. Study III for salbutamol sulphate was designed to study the effects of temperature more precisely. Three similar batches were designed that would wary from each other only with their inlet temperatures (batches 5, 6, 7, table 4). Nozzle cooling system was decided to be used in these experiments. The conducted studies are listed in Table 4. The used starting materials for further salbutamol sulphate studies (Table 4) was micronized and verified to be crystalline by PXRD and sized 1.6 μm by laser diffraction.

### 7.2.4 Budesonide DOE

From all the budesonide DOE1 points only four plus the centerpoint (twice) were produced based on the fractional factorial design presented in Figure 18. The measured points are listed in Table 4. The variation of budesonide concentration is designed according to the saturation. The usage of saturated and half saturated solutions causes the budesonide concentrations to look different in the Table 5 due to the changes in budesonide solubility in different ethanol concentrations. The starting material used for budesonide DOE1 points (Table 5) was crystalline powder.

Table 5. Budesonide DOE1 points

| | CP 1 | CP 2 | Point2 | Point4 | Point5 | Point7 |
|---|---|---|---|---|---|---|
| Ethanol (%) | 75 | 75 | 50 | 50 | 99,5 | 99,5 |
| Budesonide(%) | 1.65 | 1.65 | 0.6 | 0.3 | 2.8 | 1.4 |
| Tinlet ($^oC$) | 110 | 111 | 141 | 80 | 81 | 140 |
| Tout ($^oC$) | 71 | 68 | 87 | 45 | 53 | 89 |
| feed speed (%) | 17 | 17 | 17 | 17 | 17 | 17 |
| rotameter value (spray air flow) | 40 | 40 | 40 | 40 | 40 | 40 |
| Nozzle cooling($^oC$) | 15.1 | 15.1 | 15.1 | 15.1 | 15.1 | 15.1 |

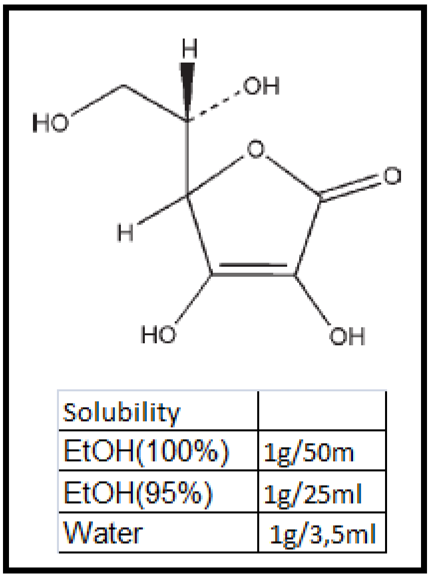
The conclusion of DOE1 was that there were no remarkable differences between the results from different test points and that all the test points appear to be crystalline in nature. This led to a need to produce XRPD- amorphous product. Literature provides a few similar studies that have successfully produced amorphous spray dried budesonide from ethanolic solutions (Mezzena *et al.* 2009; Nolan *et al.* 2009; Tajber et al. 2009a; Boraey *et al.* 2012). From these, the studies conducted by Nolan *et al.* (2009) were chosen as the primary guideline (table 6) due to the similarities with the used hardware. The further studies conducted were also designed to study additional parameters. These were designed to be conducted by producing many similar batches where different parameters were varied. The planned parameters that would be tested were the spraying air flow (test 2, 4, table 6), raw material quality (test 3, table 6) and introduction of additives (test 5, table 6). Of these spraying air flow (Das *et al.* 2010) and additives (Stieger and Liebenberg 2012) are noted to affect the crystallinity of the material. Different raw material is tested to partly validate the filtering process and test the overall differences of different batches. The inlet temperature was kept constant throughout further studies as it is clearly indicated to regulate solid state transformation (Mezzena *et al.* 2009).

Table 6. Budesonide further experiments

| | Literature | This study | | | | |
|---|---|---|---|---|---|---|
| | Nolan | Test1 | Test2 | Test3 | Test4 | Test5 |
| Ethanol (%) | 95 | 95 | 95 | 95 | 95 | 95 |
| Budesonide(%) | 1 | 1 | 1 | 1 | 2 | 0.95 |
| Ascorbic Acid(%) | - | - | - | - | - | 0.05 |
| Tinlet ($^{o}$C) | 78 | 78 | 78 | 78 | 78 | 78 |
| Tout ($^{o}$C) | 52 | 47 | 47 | 47 | 50 | 51 |
| feed speed (%) | 30 | 30 | 30 | 30 | 30 | 30 |
| rotameter value (spray air flow) | 40 | 41 | 55 | 41 | 30 | 40 |
| Nozzle coolig ($^{o}$C) | - | - | - | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| Starting material | microniz. | crystall. | crystall. | microniz. | microniz. | microniz. |
| PXRD | crystall. | crystall. | crystall. | crystall. | crystall. | crystall. |
| size (μm), median | 1.4 | 88 | 88 | 1.6 | 1.6 | 1.6 |

The first experiment (Test 1) was designed to be an exact duplicate of the original experiment whereas the rest were modified from the original by varying different parameters (varied parameters are shaded grey) (Table 6). Test 2 experiment was based on the assumption that smaller droplets would dry much quicker and that there would not be enough time for crystallization (Masters 2002). Test 3 was based on the assumption that the original dissolution speed of budesonide (Test 1) would be inadequate and leave some minor crystalline seeds into the solution. This was tested by changing the raw material into a micronized quality. In Test 4 it was checked whether the increase in solid concentration and the increase in droplet size would increase the level of crystallinity. Test 5 was based on the assumption that additives of similar structure would disturb the crystallization process. Ascorbic acid (Fig. 19) was chosen to be the additive because of its similarities in structure and solubility.



| Solubility | |
|---|---|
| EtOH(100%) | 1g/50m |
| EtOH(95%) | 1g/25ml |
| Water | 1g/3,5ml |

Figure 19. Structure and solubility of ascorbic acid (Rowe *et al.* 2009)

## 7.3 Preparation of mixtures

The mixtures of ethanol and water were prepared *in situ* if no commercial products were available. The APIs were added after the blending of the solvents and allowed to blend for approximately 24 hours which was concluded to be a compromise between the time available and the values previously used (Ali *et al.* 2010). To produce saturated solutions an amount of 10% excess API was usually added. This precipitated excess API, if included, was filtered just prior to the spray drying by using a funnel and filter paper (Munktell analytical filter paper, grade 1F, diameter size 150 mm, Munktell Filter AB, Grycksbo, Sweden). If spray-dried feeds were intended to be suspensions, the extra solid content was weighted and added after filtering.

## 7.4 Spray drying

All the experiments were conducted with Büchi Spray dryer B-290 (Buchi Labortechnik AG, Flawil Switzerland). The used model had a small collection vessel, 1.5mm nozzle cap and 0.7 mm diameter nozzle but otherwise it was operated with standard equipment provided by Büchi. Due to the ethanol content of the feeding mixtures the spray dryer had to be operated in closed mode combined with Inert loop B-295 condensation unit (Fryka-Kältetechnik GmbH, Esslingen Germany) (Fig. 20). The gaseous drying medium was nitrogen. The system used was also later accompanied with a water dispenser (Jumbo F25) to cool down the spray drying nozzle. During the production the spray dryer was situated in a temperature (about $22^{o}$C) and moisture (below 20% RH) controlled laboratory. The used bag filter material was insufficient for particle recovery.

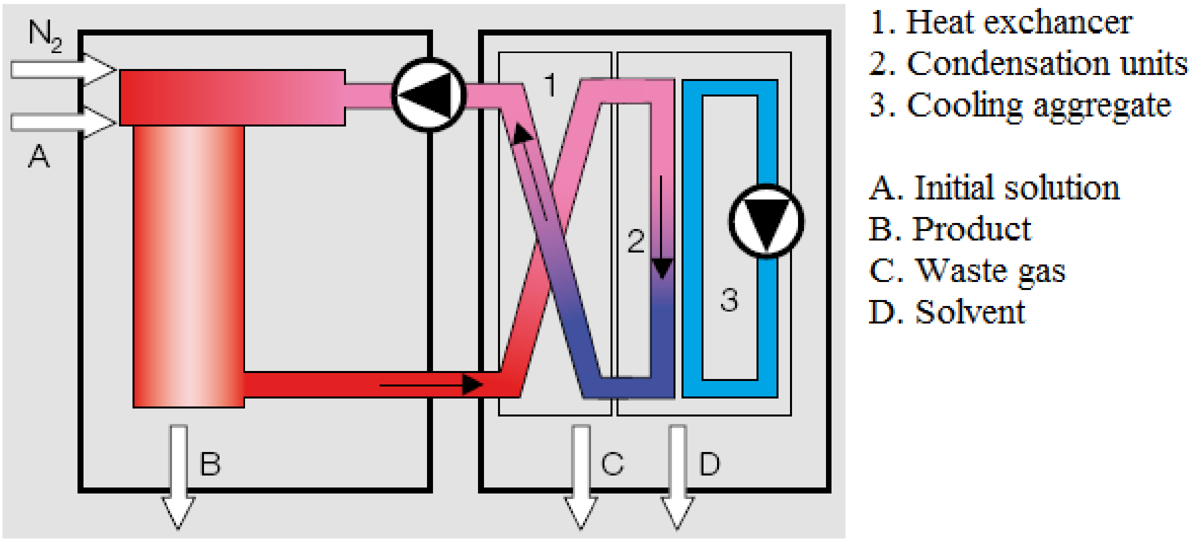


Figure 20. Schematic drawing of a spray dryer combined with inert loop. (www.buchi.comTMS, modified from the original)

## 7.5 Annealing

Some of the spray-dried salbutamol sulphate batches were used to study annealing procedure. The goal was to alter the produced round amorphous particles into similarly sized and shaped crystalline particles. This was first tried for an amorphous batch (Batch 2 from Study I, Table 4) in a petri dish for 3 days in a water vapour annealing box of 65% relative humidity. The values were chosen on the basis of AstraZeneca´s unreported study (AstraZeneca 2009) but they were in good line with the results of Brodka-Pfeiffer *et al.* (2003). The annealing time needed appears to be closely related to the other values used.

After the crude tests, a more elaborate small scale flow-annealing system (Fluxus, AstraZeneca, Sweden) was used to anneal salbutamol sulphate. The material used in Fluxus-experiments was amorphous Batch 7 from Study III (Table 4). The values used in the flow-annealing system are listed in the Table 6. Due to the intense agglomeration observed in Batch 1 (Table 7), slightly lower values were chosen for Batch 2. It was also observed that the annealing procedure did not require 48 hours time as observed by Adilovic et al. (2012). The new values produced a lot less agglomerated powder, which was unfortunately nearly

XRPD amorphous. The conclusion from these results was to increase the temperature and not the relative humidity for Batch 3 (table 7). It is known that compared to relative humidity, temperature has less effect on particle size in annealing (Brodka-Pfeiffer *et al.* 2003).

Table 7. The used flow annealing values

| | Batch 1 | Batch 2 | Batch 3 |
|---|---|---|---|
| T ($^{o}$C) | 30 | 25 | 30 |
| RH | 60 | 55 | 55 |
| Preheating (h) | 2 | 1 | 2 |
| TvapourGenerator | 23.4 | 15.2 | 19.8 |
| Drying | 1 | 1 | 1 |
| Annealing Time (h) | 48 | 24 | 13 |
| turning time: (sec) | 8 | 8 | 16 |
| vibration time : (sec) | 5 | 5 | 10 |
| vibration delay: (sec) | 3 | 3 | 6 |
| sample amount | 1.9 | 2 | 2.1 |
| FlowVapourGener (l/min) | 0.5 | 0.5 | 0.5 |

Budesonide annealing was conducted for batch test 3 (Table 6). Small amount of material from batch test 3 was applied to two XRPD-plates. These plates were first measured with XRPD and then put in two different annealing boxes. The other box contained ethanol salt solution that corresponded to 74% relative ethanol activity and the other box contained solution that provided 100% relative ethanol activity. The samples were measured five times at different time intervals (0, 1st, 4th, 7th and 16th day). The raw materials (Crystalline raw material and micronized raw material) were used as control samples and they were put in the 100% relative ethanol activity box. The control samples were measured four times (0, 1st, 4th and 13th day)

## 7.6 Characterization

### 7.6.2 Particle size distribution

Particle size distribution was analyzed with laser diffraction (Mastersizer 2000, Scirocco 2000, Model MS2000, Malvern Instruments, Worcestershire UK) using a dry powder method. A small amount of powdered sample (less than 1 g) is introduced to the analyzer by using the scirocco attachment. Air pressures from 1 to 3 bars were tested to validate a suitable pressure for repeatable tests for each sample. Three parallel tests were done when the sample amount was adequate. The feed rate for the powder was varied from 10 mm/s to 50mm/s depending on the powder flowability. The measured $D_{10}$, $D_{50}$ and $D_{90}$ values were reported and in addition the Span was calculated according to the Equation 3.

$$Span = \frac{D_{90} - D_{10}}{D_{50}} \tag{3}$$

### 7.6.3 Crystallinity

The X-ray powder diffraction (XRPD) patterns for the samples were analyzed with Diffractometer D8 (Bruker AXS, Karlsruhe, Germany, PXRD1) and with Philips PANalytical X´Pert (PXRD2). The PXRD1 was used for all other analyses, save the ethanol atmosphere annealing studies for budesonide. This was due to the inherent intolerance of the sample holders in the PXRD1 for ethanol atmosphere. A small amount of the samples measured were carefully spread into individual sample holders. The measurements were generally carried out immediately after the production.

The Bruker AXS Diffractometer D8 (PXRD1) was operated with a position sensitive detector (PSD) LynxEye with a 3° PSD-window. The Cu anode X-ray tube was operated at 30 kV and 50 mA. Measurements were generally taken from 2.4° to 50° with a step size of 0.02 (°2 Theta) and a dwell time of 0.5 s per step. Sample holders were made of plastic with a silicon plate.

The Philips PANalytical X´Pert (PXRD2) was operated with a 1.0◦ dispersion slit and a 0.1◦ receiving slit. The Cu anode X-ray tube was operated at 45 kV and 40mA. Measurements were generally taken from 2.4° to 50° with a step size of 0.013 (°2 Theta). The measuring time was 44.37 sec. Sample holders were assembled from a silicon plate and a steel ring before measurements. These sample holders contained no glue or plastic and were able to withstand organic solvents like ethanol.

### 7.6.4 Particle morphology

The morphology of each sample was studied using a scanning electron microscope, SEM, (Quanta 200, FEI Company, Eindhoven, The Netherlands) at high vacuum mode. Images were taken from random locations. Prior to imaging, a small amount of each sample was dispersed on a carbon sticky tab and coated with gold. The thin gold coating was applied on the surface with a sputter coater (108 auto sputter coater, Cressington scientific instruments Ltd, Watford, UK) in argon atmosphere at 20 mA for 100 seconds.

# 8 RESULTS AND DISCUSSION

## 8.2 Raw materials

The raw materials used, two types of budesonide and one type of salbutamol sulphate, were characterized by using the same measurement techniques as for the products. These included PXRD, SEM and laser diffraction.

### 8.2.2 Particle size distribution

Particle size distribution (Table 8) was quite similar in both micronized batches, whereas the crystalline batch was considerably larger sized. The micronized quality is within the respirable size range (Newman *et al.* 2009).

Table 8. Particle size distribution of APIs

| | D10 (μm) | D50 (μm) | D90 (μm) |
|---|---|---|---|
| Salbutamol sulphate | 0.7 | 1.5 | 3.1 |
| Budesonide | 9.7 | 88.7 | 254 |
| Budesonide, micronized | 0.5 | 1.6 | 3.8 |

### 8.2.3 Crystallinity

The PXRD studies for budesonide show a typical crystalline pattern (Phamand and Wiedmann 2000; Steckel *et al.* 2004; Mezzena *et al.* 2009; Naikawade *et al.* 2009; Nolan *et al.* 2009; Tajber *et al.* 2009a; Kumon *et al.* 2010; Carr *et al.* 2011; Boraey *et al.* 2012; Kubavat *et al.* 2012) (Fig. 21). The differences in peak intensities can possibly be explained by the presence of amorphous material in the micronized raw material (Fix and Steffens 2004; Grisedale *et al.* 2011) or size differences (Grisedale *et al.* 2011).

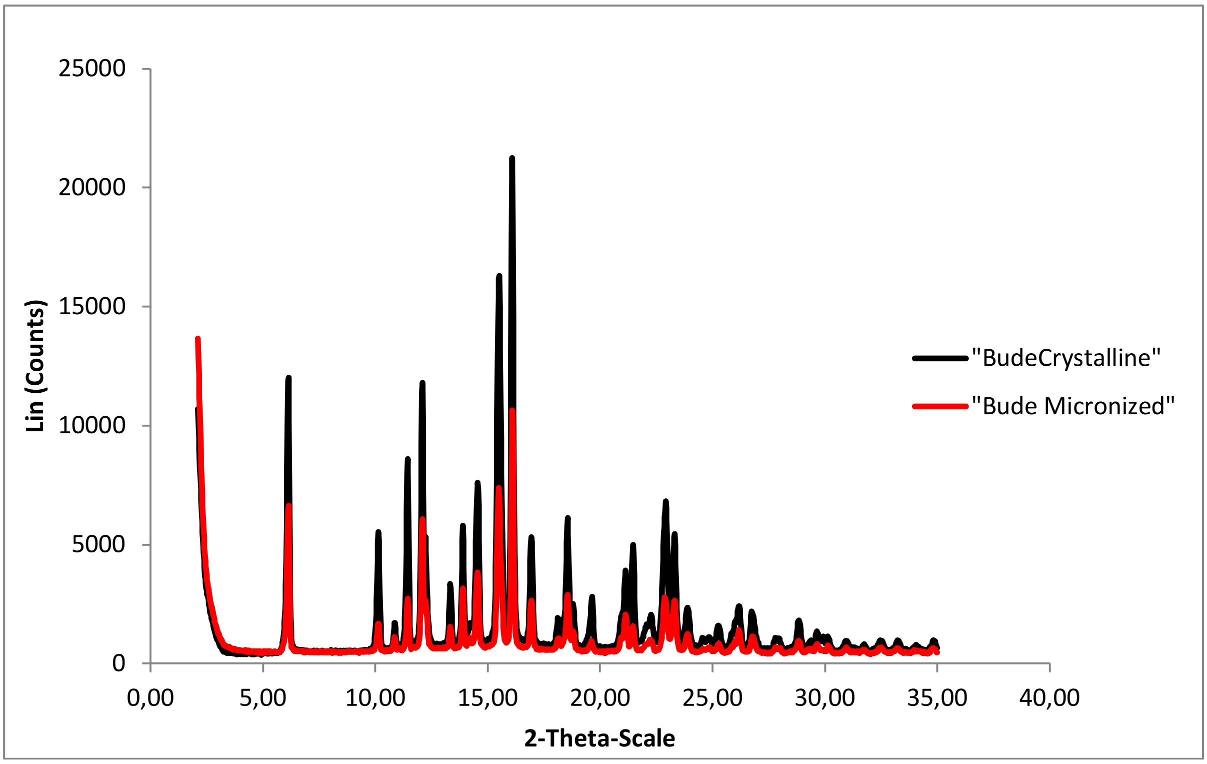


Figure 21. XRPD diffractograms of budesonide raw materials. The black line is crystalline budesonide ($D_{50}$=88.7μm) and the red line is micronized crystalline budesonide ($D_{50}$=1,6μm)

The PXRD pattern of the used salbutamol sulphate was also crystalline (Chawla *et al.* 1994; Ward *et al.* 1995; Columbano *et al.* 2002; Palacio *et al.* 2007; Palacios *et al.* 2007; Raula *et al.* 2008; Balani *et al.* 2009; Dhumal *et al.* 2009; Balani *et al.* 2010; Grisedale *et al.* 2011; Mueannoom *et al.* 2012; Traini *et al.* 2012). It is good to acknowledge, however, that it was micronized and therefore might contain partly amorphous material (Grisedale *et al.* 2011) (Fig. 22). This XRPD pattern resembles closely form I polymorphic type characterized by Palacio *et al.* (2007).

When interpreting XRPD patterns it is necessary to acknowledge the limits of the method used. The XRPD has been verified to detect less than 1% amorphous contents in crystalline solids (Chen X. *et al.* 2001; Fix and Steffens 2004) and less than 0.5% crystalline content in amorphous solids (Fix and Steffens 2004). These results are dependent on the optics and the sample preparation technique used. In addition to these limitations it is good to keep in mind that similar XRPD pattern can be produced by different solid state forms of the same substance (Bates *et al.* 2006) or two totally different substances (Brittain 2003). It is therefore suggested that another confirming technique like differential scanning calorimetry (DSC) should be used to verify XRPD results (Brittain 2003).

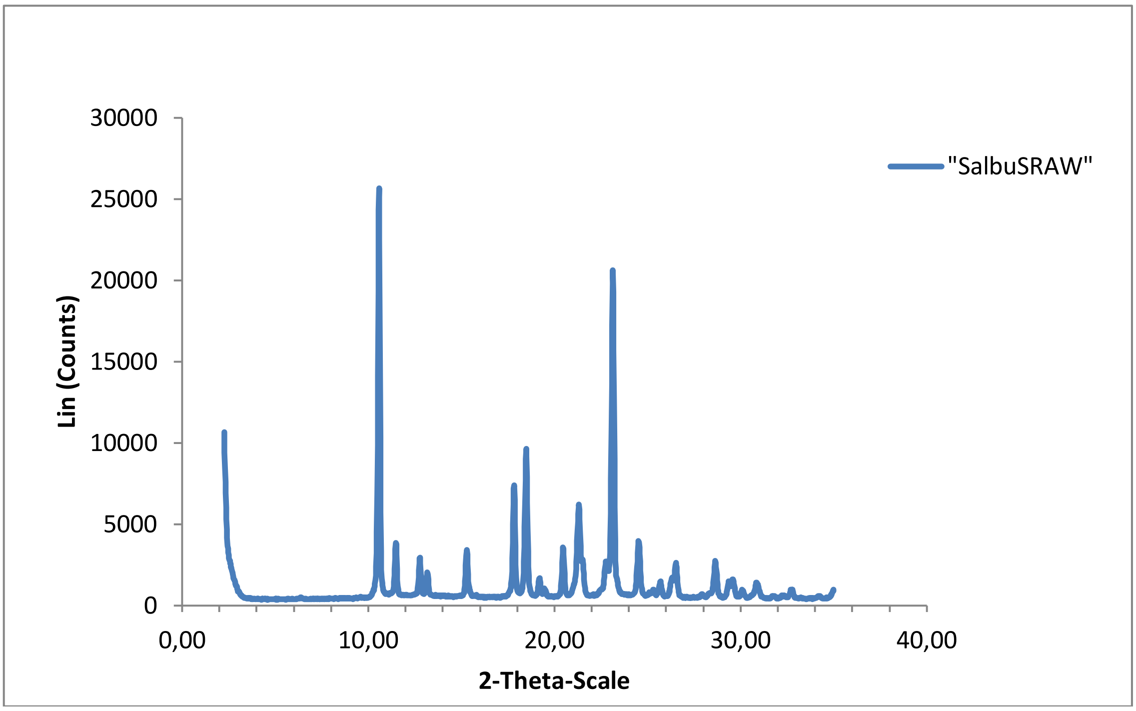


Figure 22. XRPD diffractograms of salbutamole sulphate raw material.

Annealing the budesonide raw materials in 100% REtOH atmosphere and room temperature (22$^{o}$C) for 120h did not change the XRPD profile remarkably, but slightly bigger changes can be observed in the peaks of the micronized batch (data not shown). These results support the measurements done by Grisedale *et al.* (2011).

### 8.2.4 Morphology

Particle size differences can be easily detected from the SEM pictures of budesonide raw materials (Fig. 23). Figure 23 also suggest that the unmicronized budesonide could be crystalline but this needs to be confirmed with additional measurement techniques.

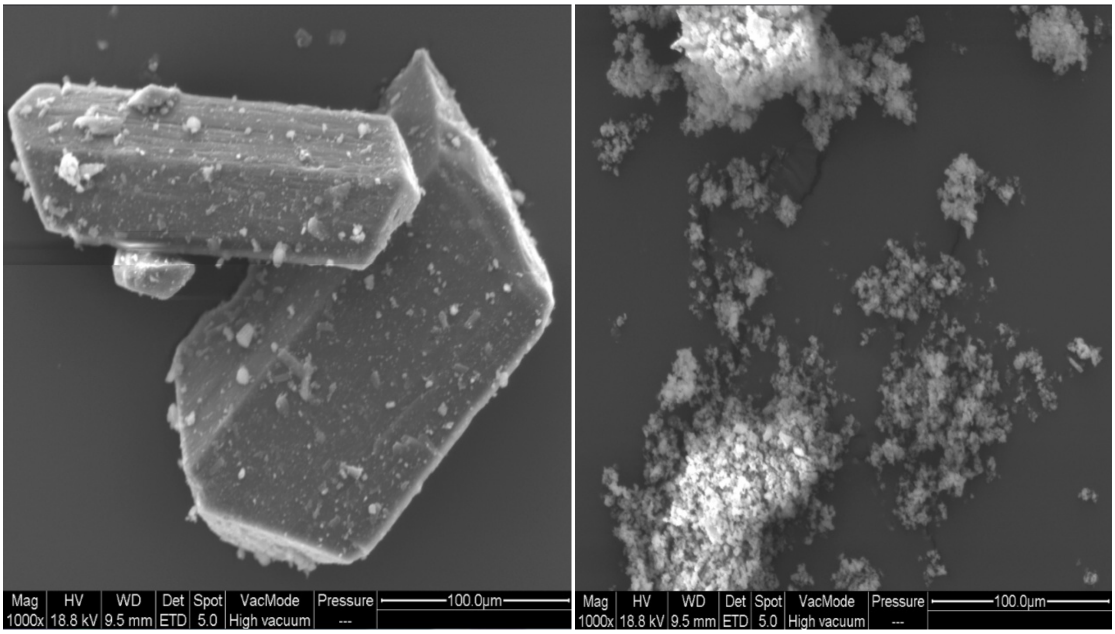


Figure 23. SEM pictures of unmicronized budesonide raw material (left) and micronized budesonide raw material (right).

## 8.3 Salbutamol sulphate DOE1

The points listed in Table 3 were the points that were designed to be measured. However, due to the technical challenges and the early learning phase it later became evident that not all the designed points were feasible. Due to these challenges point 4 was repeated (Point 4b) and point 7 had to be excluded from the planned experiments. Challenges that were encountered for the production of point4 were the apparent total blocking of the bag filter in the early phase of the spray drying and the overestimation of the product yield. As the research went further it became evident that the product yield for the point 7 would be considerably low due to the low yield recovered from the point 5 that had two times higher solid content.

### 8.3.2 Yield

The yields for the salbutamol sulphate DOE1results (Table 9) are quite varying. The reasons for this are the two challenges pointed out in the previous chapter and the variation in the solubility of the salbutamol sulphate in different solvent mixtures. Point2 (Table 9) which gave a reasonable yield, was produced from a saturated solution and from a solvent mixture to which salbutamol sulphate had a good solubility. The successfully produced batch 4 (Point 4b) emphasizes the fact that one must have large enough batches to minimize the relative effects of some of the major factors that decrease the yield: deposition in the walls of the spray drier and adsorption in the surface of the bag filter.

Table 9. Salbutamol sulphate DOE1 yields

| | Yield (g) | Yield (%) |
|---|---|---|
| Point2 | 0.88 | 27 |
| Point4b | 2.7 | 66 |
| Point5 | 0.14 | 9 |
| CP1 | 0.16 | 7 |

### 8.3.3 Particle size distribution

From the results presented in Table 10 the only viable candidate for further development seems to be Point4b because it has the particle size distribution closest to the 1-5 μm particle size that is considered essential for deep lung penetration (Bechtold-Peters *et al.* 2007). The small yields (Table 9) affected the credibility of the particle size measurements (Table 10) due to the lack of decent amount of parallel samples. The high $D_{90}$ values (Table 10) are caused by an attempt to improve low yields by recovering material that had fused in the walls of the cyclone. This material was effectively fused with cyclone and had to be mechanically recovered in considerably large particles.

Table 10. Salbutamol sulphate DOE1 particle size distribution

| | $D_{10}$ | $D_{50}$ | $D_{90}$ | Span |
|---|---|---|---|---|
| Point2 | 0.95 | 4.2 | 150 | 36 |
| Point4b | 0.74 | 2.7 | 5.7 | 1.8 |
| Point5 | 0.6 | 6.9 | 89 | 13 |
| CP1 | 0.7 | 2.6 | 80 | 31 |

### 8.3.4 Crystallinity

Figure 24 shows that the spray dried batches for salbutamol sulphate DOE1 were all amorphous in XRPD. This finding that all the produced batches were amorphous confirms the conclusion that the batch point 4 (table 3) was the best candidate for further studies under these circumstances with its superior yield and suitable size distribution compared to other batches.

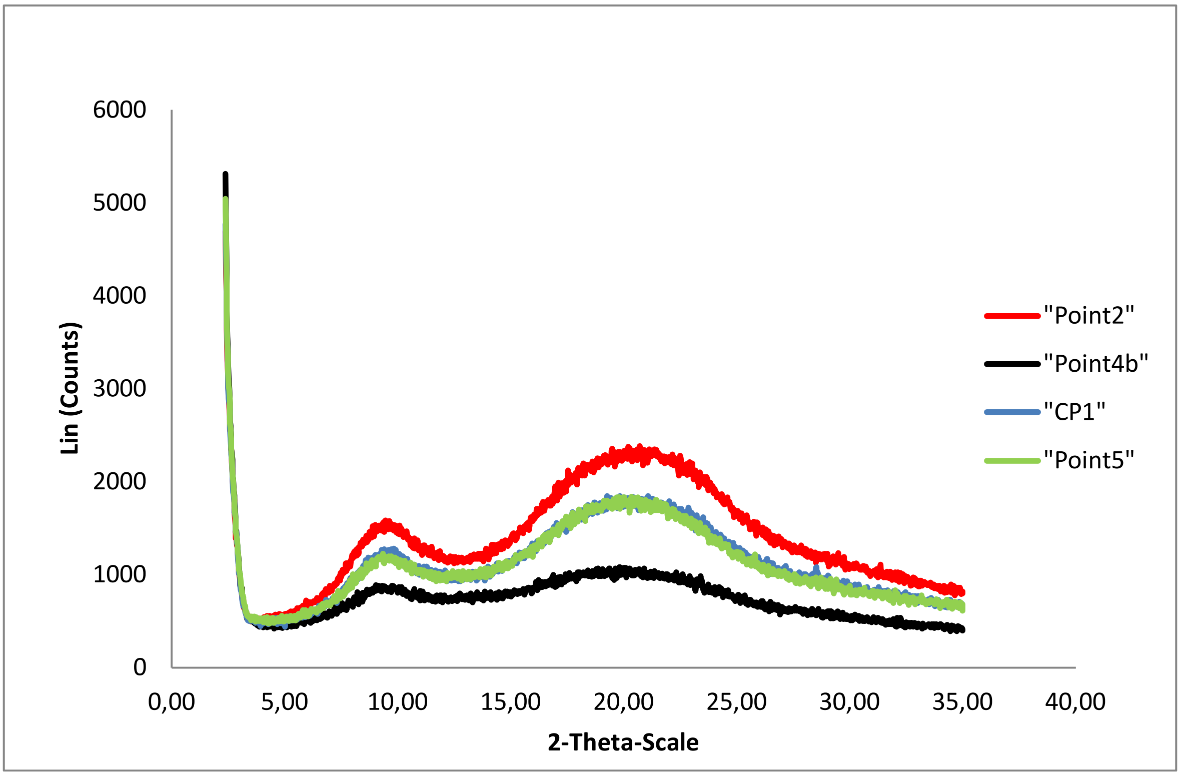


Figure 24. XRPD diffractograms of salbutamol sulphate DOE1 batches

## 8.4 Salbutamol sulphate -effects of temperature and concentration

### 8.4.1 Yield

From the results (Table 11) we can conclude that the yield percentage increases slightly when the raw material amount is increased. There are no significant differences between the relative yields for different batches. These yields can be considered reasonably high according to literature (Bögelein and Lee 2010).

Table 11. The further studies yield for salbutamol sulphate

| | Yield (g) | Yield (%) |
|---|---|---|
| 1 (I) | 5 | 87 |
| 2 (I) | 7.1 | 92 |
| 3 (II) | 4.9 | 79 |
| 4 (II) | 5.3 | 79 |
| 5 (III) | 6.6 | 86 |
| 6 (III) | 8.7 | 89 |
| 7 (III) | 8.9 | 81 |

### 8.4.2 Particle size distribution

It can be seen that for Studies I and II (table 12), the excess solid content seems to have increased the particle size. Similar results are found in other studies (Elversson *et al.* 2003; Corrigan *et al.* 2004; Mosen *et al.* 2004; Elversson and Millqvist-Fureby 2005a; Maury *et al.* 2005; Sansone *et al.* 2009; Amaro *et al.* 2011; Gallo *et al.* 2011; Buchi process parameters guide 2012). The same phenomenon is also seen in Study III but now the particle size has increased in the function of the inlet temperature. In the literature size variation in particle size is said to increase (Fang *et al.* 2012) but the effects on particle size are mixed. The increase in temperature was found to increase particle size by Fu *et al.* (2013) but not by Maas *et al.* (2011). These results could indicate that temperature has a substance specific effect on particle size.

Table 12. Particle size distribution for further studies

| | $D_{10}$ (μm) | $D_{50}$ (μm) | $D_{90}$ (μm) | Span |
|---|---|---|---|---|
| 1 (I) | 0.65 | 2.6 | 5.9 | 2 |
| 2 (I) | 0.73 | 2.9 | 6.8 | 2.1 |
| 3 (II) | 0.64 | 2.5 | 6.2 | 2.2 |
| 4 (II) | 0.64 | 2.8 | 7 | 2.3 |
| 5 (III) | 0.56 | 2.2 | 5.6 | 2.3 |
| 6 (III) | 0.58 | 2.3 | 5.7 | 2.3 |
| 7 (III) | 0.72 | 2.8 | 6.5 | 2.1 |

### 8.4.3 Crystallinity

The salbutamol sulphate batches from Study I were both amorphous and there were no significant differences between the two batches (Fig. 25). These results suggest that the product is not sensitive to the composition of the feedstock in regard to the solid content. Therein it does not support the findings of Alves and Santana (2004) and Bianco *et al.* (2012). Batch 1 (Fig. 25) was produced by spray drying a saturated solution and Batch 2 (Fig. 25) was produced from the same saturated solution with 10% added excess solid to form a suspension. Spray drying seems to convert suspended material into the amorphous state in addition to the dissolved material. This finding was also observed by Chidavaenzi *et al.* (1997), who suggest the reason for this phenomenon to be pressure induced milling effect and excess nozzle heating that together increase the apparent solubility.

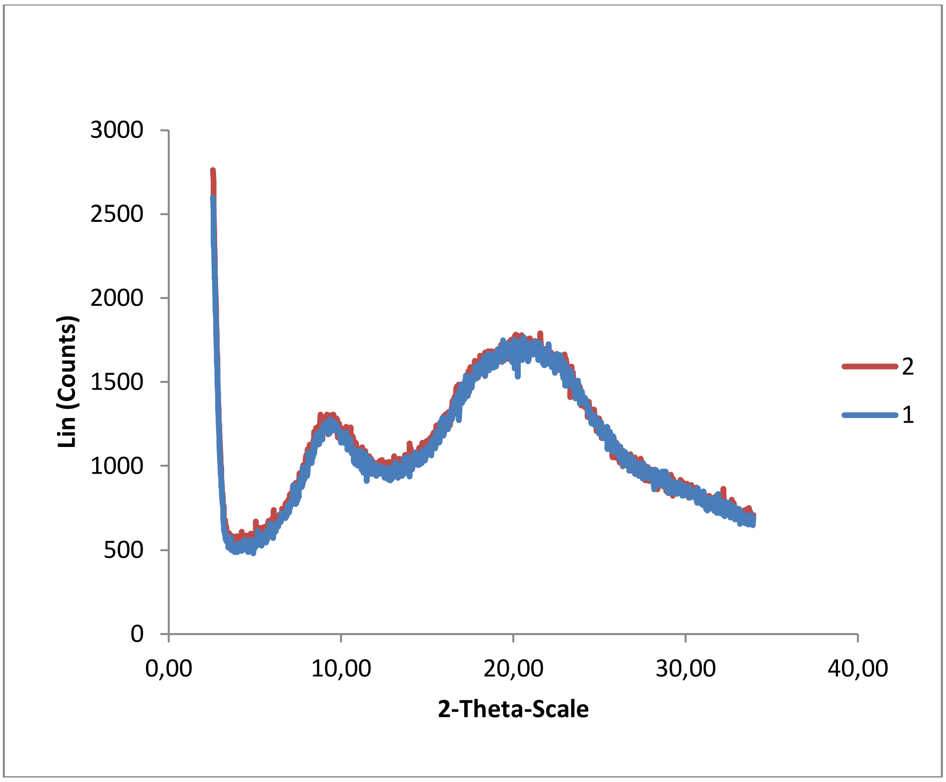


Figure 25. XRPD diffractograms of salbutamol sulphate Study I, Batches 1 and 2

The results in Figure 26 prove that the phenomenon was at least partly dependent on nozzle temperature as presented by Chidavaenzi *et al.* (1997). The results also show that the peaks were higher in the product that was produced from higher solid content suspension but not as high as in original raw salbutamol sulphate (Fig. 22). This could indicate that the spray drying process does not considerably increase the amorphicity of the suspended material when nozzle cooling is used. This is probably due to two reasons: firstly precipitation is energetically more favorable state than high supersaturation (Stieger and Liebenberg, 2012) and secondly the suspended crystalline material is energetically more stable than amorphous material. Therefore, if the solubility remains unchanged the excess solid material will be little affected. The higher peaks for the Batch 4 (Fig. 26) could probably be caused by the larger quantity of the suspended material and by the observed larger particle size (table 12) as pointed out by Grisedale *et al.* (2011).

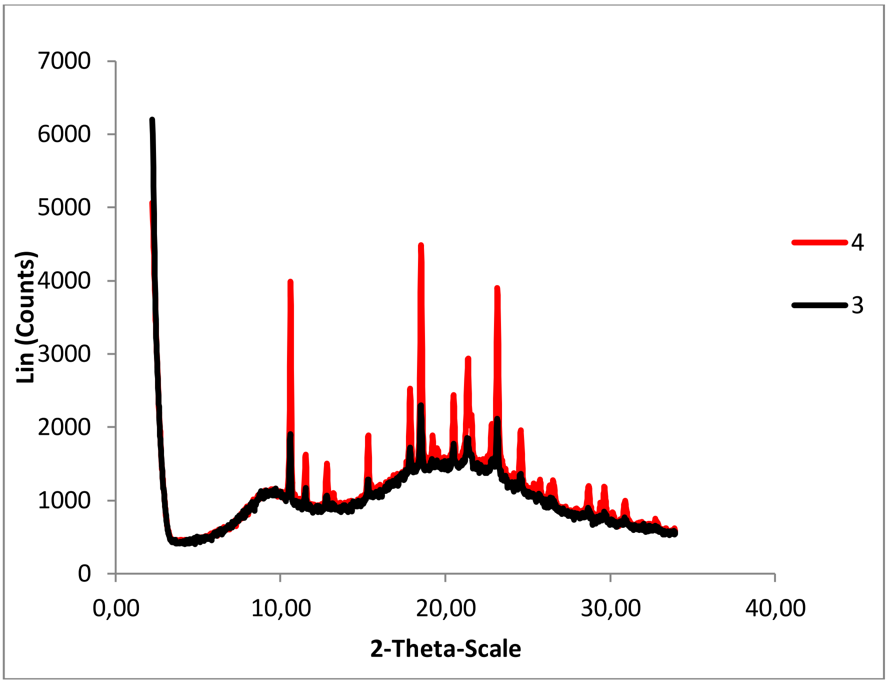


Figure 26. XRPD diffractograms of salbutamol sulphate study II, Batches 3 and 4

The results (Fig. 27) show that there were no significant differences in the crystallinity of these three batches when measured with XRPD. This is interesting as Islam *et al.* (2010) found that temperature might increase crystallinity. Perhaps the temperature range was inadequately narrow or crystallinity is more dependent on material than on process parameters.

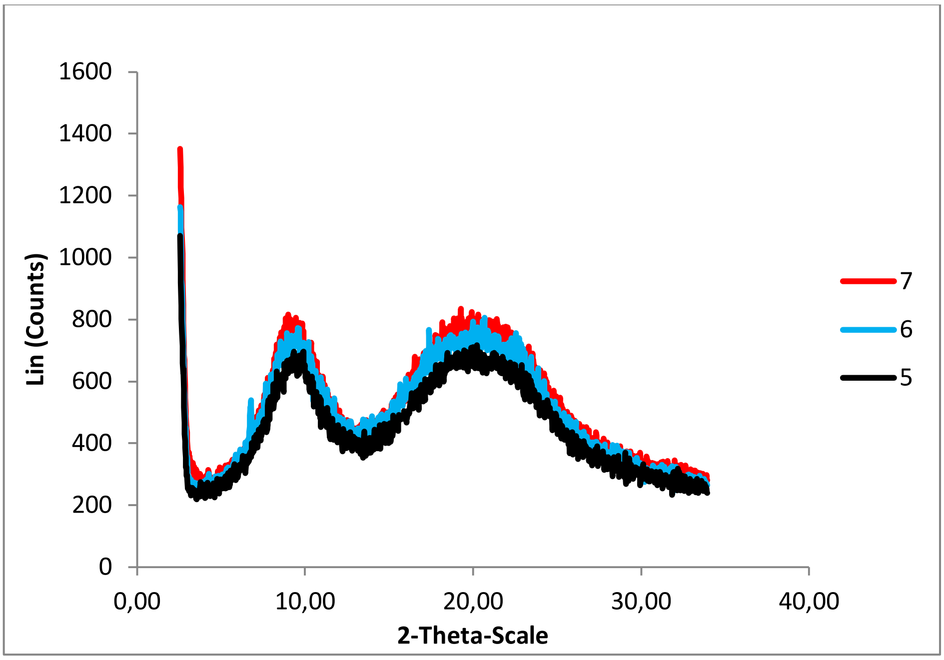


Figure 27. XRPD diffractograms of salbutamol sulphate further Study III, Batches 5, 6 and 7

### 8.4.4 Morphology

Figure 28 shows that the spray dried salbutamol sulphate particles in Batch 2 (Study I, table 4) were round, smooth and about 5 μm in diameter. Figure 29 shows that both samples in Study II (table 4) were similarly structured and sized as particles in Study I (table 4).

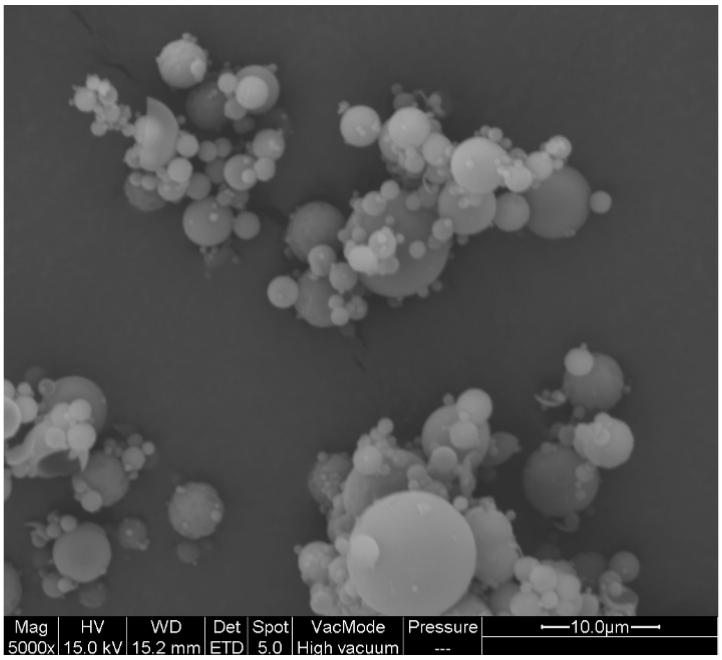


Figure 28. SEM pictures of salbutamol sulphate Batch 2 from Study I (table 4)

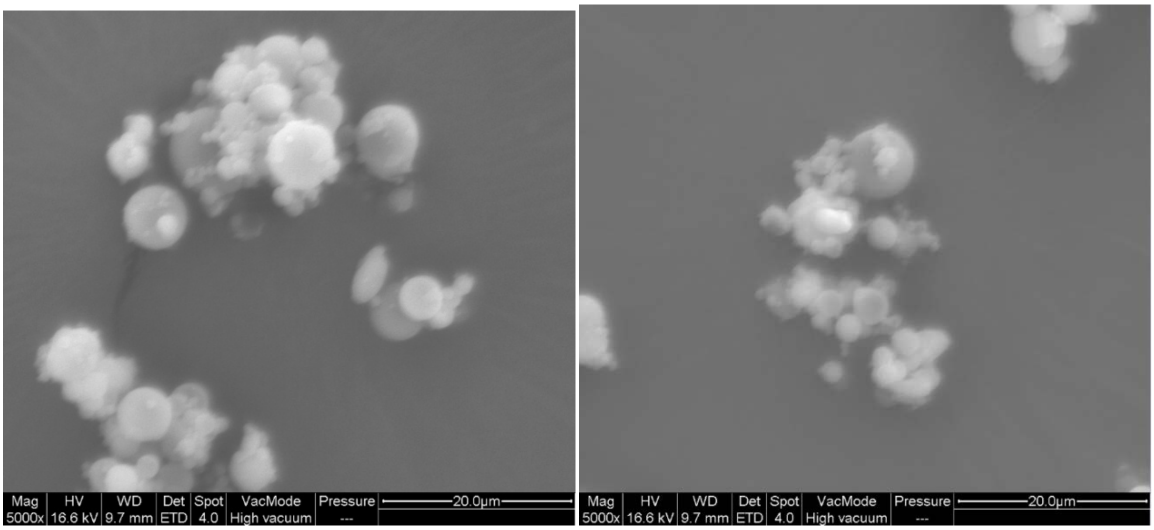


Figure 29. SEM pictures of salbutamol sulphate Batch 3 (left) and Batch 4 (right) from the Study II (table 4)

Study III (Fig. 30) produced similarly round particles around size 5 μm diameter as Study I (Fig. 28) and II (Fig. 29). There can, however, be slight differences observed between the highest (Batch 7) and the lowest (Batch 5) inlet temperature batches. Some of the particles in Batch 5 (Fig. 30) seem not to have a smooth surface but a quite wrinkled instead. This may indicate that the lower drying temperature has allowed the samples to dry slower, shrink in size and form dense particles (Masters 2002) with larger surface area. This conclusion is not entirely supported by literature because Littringer *et al.* (2012), Fang *et al.* (2012) and Maas *et al.* (2011) produced opposite results. Most probably the results are dependent on the characteristics of the spray-dried substance.

In Study III (Fig. 30) the higher inlet temperature has produced smooth particles with possibly lower density, hollow structure and less durability for mechanical handling (Masters 2002). Though the temperature seemed not to affect crystallinity, it had some interesting effects on the morphology of the particles that might be useful for inhalation formulations. More corrugated particles have been found to produce more fines during the inertial impaction when compared with smoother particles (Adi *et al.* 2013). Larger surface area would also possibly provide faster dissolution time and on the other hand hollow particles would be beneficial as phagocytic clearance in the lungs needs to be avoided (Bechtold-Peters *et al.* 2007, Newman *et al.* 2009).

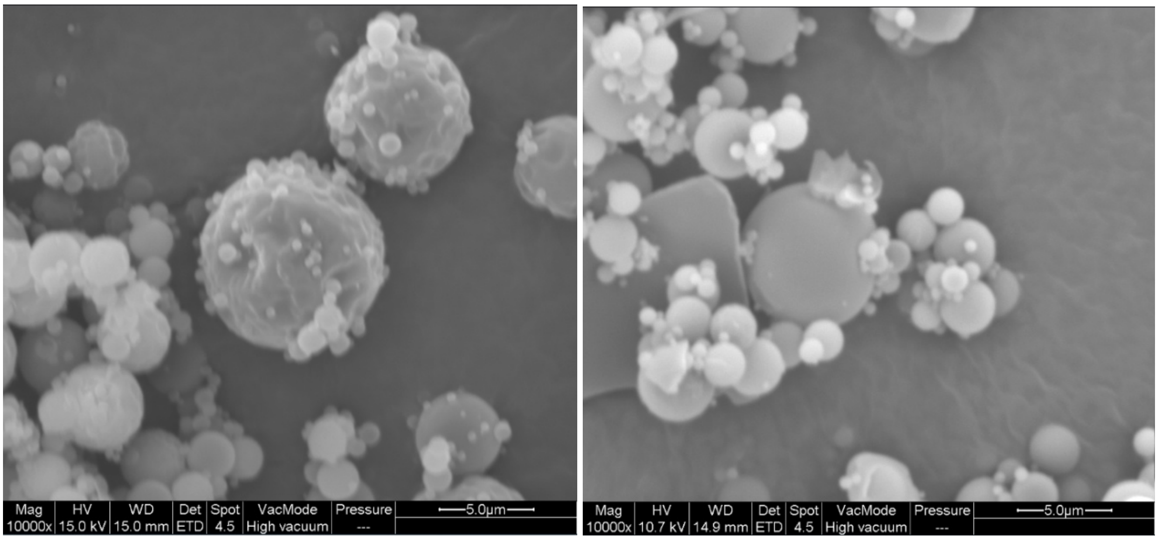


Figure 30. SEM pictures of salbutamol sulphate Batch 5 (left) and Batch 7 (right) from the Study III (table 4)

## 8.5 Salbutamol sulphate annealing

### 8.5.1 Crude annealing in a box

Spray dried salbutamol sulphate that was initially amorphous powder had turned into larger agglomerates that had partly stuck on the surface of the annealing dish. The particle growth was verified with particle size measurements (Table 13) and crystallinity with XRPD (Fig. 31).

Table 13. Particle size distributions for spray dried and annealed salbutamol sulphate batch.

| | $D_{10}$ | $D_{50}$ | $D_{90}$ | Span |
|---|---|---|---|---|
| SBS Spray dried (µm) | 0.73 | 2.9 | 6.8 | 2.1 |
| SBS Annealed (µm) | 360 | 970 | 1600 | 1.3 |

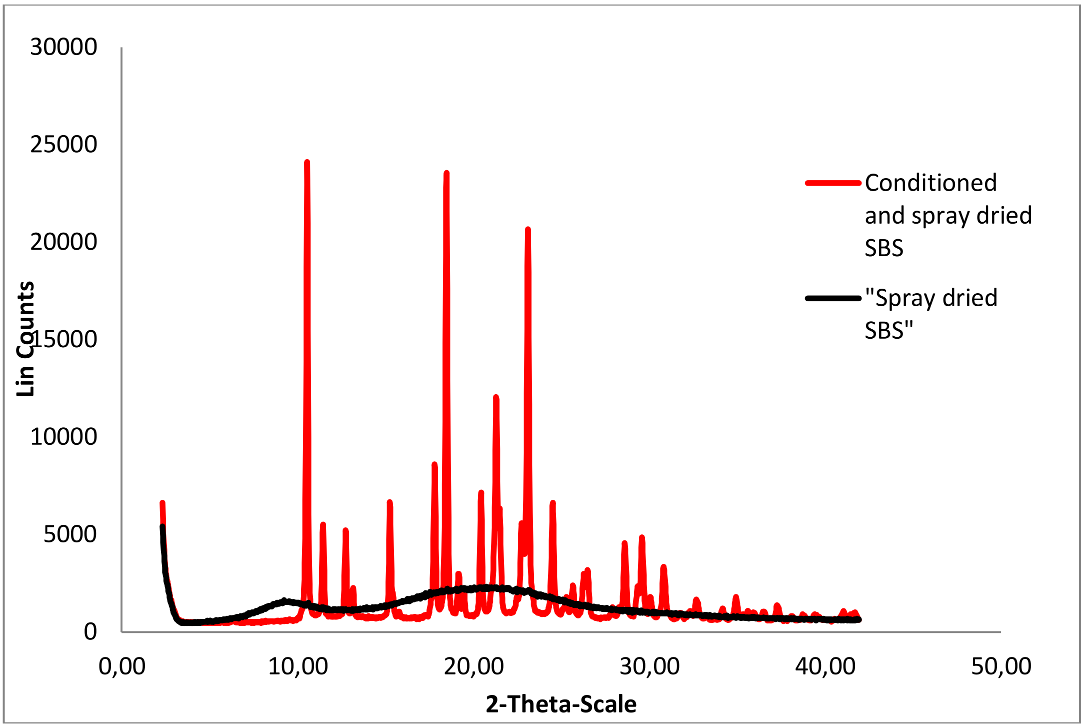


Figure 31. XRPD diffractograms of salbutamol sulphate annealed with the crude method.

The SEM pictures (Fig. 32) confirm the particle size growth noted in the particle size distribution measurements (Table 13). Particle growth in annealing has previously been recognized by Brodka-Pfeiffer *et al.* (2003), who also found it rather challenging to avoid.

The left part of Figure 32 shows that the particle has been damaged and seems to have two distinctly different regions: surface and core. This finding could indicate that these annealed particles are not hollow. It also raises a question whether the two regions are equally crystalline and formed of the same polymorph. The damage for the particle in left side of the Figure 32 is probably caused by the necessary detaching of particles from the annealing dish.

The conclusion from this crude annealing method was that fully XRPD amorphous salbutamol sulphate can be annealed to a XRPD crystalline form in three days time under the used conditions. The challenges are the uncontrolled particle growth and the process dependency on different variables.

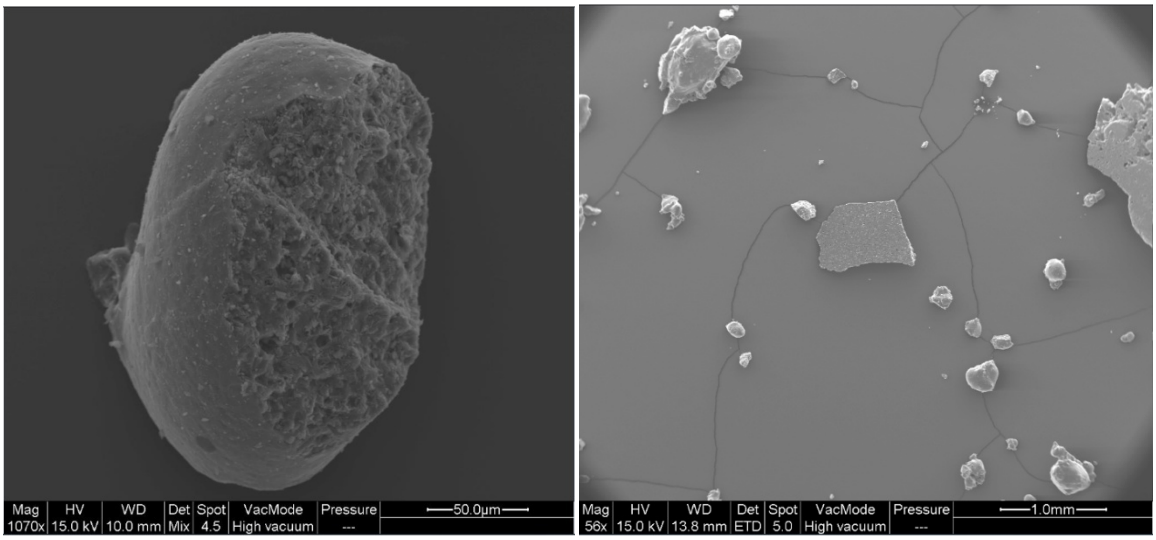


Figure 32. SEM pictures of annealed salbutamol sulphate particles, one particle (left), overview (right).

### 8.5.2 The utilization of small scale flow annealing equipment

The result for the Batch 1 annealing was XRPD crystalline agglomerate (Fig. 33) with little or no powder. The changes made for Batch 2 (table 6) produced a lot less agglomerated powder, which was unfortunately nearly XRPD amorphous (Batch 2, Fig. 33). These results were thought to be caused by too low process temperatures in Batch 2. Though this was proven wrong with the Batch 3, what produced tightly aggregated non-crystalline material in higher temperature (Batch 3, Fig. 33). The reason for the quality produced in Batch 3 might be related to the less intense mechanical handling (slower turning time, table 7) that might have limited the mixing efficiency of the processed powder.

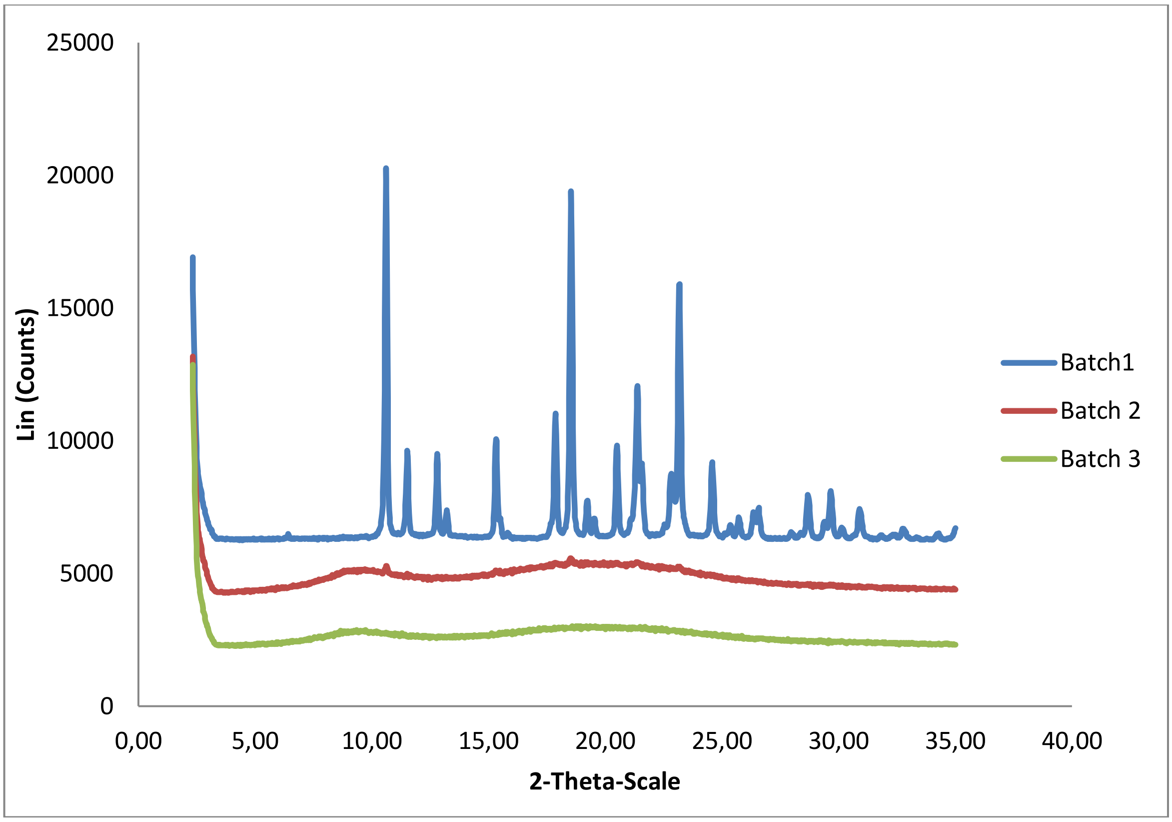


Figure 33. XRPD diffractograms of salbutamol sulphate in flow annealed samples

## 8.6 Budesonide DOE1

### 8.6.1 Yield

The DOE1 batches of budesonide were all less than 3 g each. This, the cohesive nature of budesonide (Boraey *et al.* 2012) and the small particle size caused the yields (Table 14) to remain small. Varying amounts of product ended in the top of the cyclone and into the bag filter. Due to the current setup they were not harvested (the top of the cyclone was hard to reach and the used bag filter type was not designed for collecting purposes). The low yield in spray drying pure budesonide powders can be a challenge (Boraey *et al.* 2012) and should therefore be anticipated.

Table 14. Budesonide DOE1 yields

| | Yield (g) | Yield (%) |
|---|---|---|
| Point2 | 0.34 | 27 |
| Point4 | 0.44 | 17 |
| Point5 | 0.66 | 23 |
| Point7 | 0.24 | 17 |
| CP1 | 0.25 | 24 |
| CP2 | 0.46 | 34 |

The highest yield in grams (Point 5) is partly explained by the good solubility of budesonide in saturated solution at this point (Table 14). Apparently the half saturated points (Point 4 and Point 7) have lower yield percentages than the saturated points (Point 2 and Point 5). This might also be the result of the lower initial solid content.

### 8.6.2 Particle size distribution

Particle size distribution for the budesonide DOE1 batches are listed in Table 15. The low yields and especially the bag filter blocking might indicate a larger amount of smaller size fractions in the product than measured with laser diffraction. For the lower yield the material had to be scratched from the surfaces of the cyclone and the main collection vessel. This may have affected the quality of the products. The amounts produced were also inadequate for particle size measurements, because they did not provide enough material for many parallel measurements. The results in Table 15 show a trend where the chosen three parameters (ethanol concentration, inlet temperature and solid content) seem to have little effect on the particle size and particle size distribution. The deviation of the $D_{90}$ value for point7 might be explained by agglomerates produced by scratching the material from the glass surfaces. Further studies are needed to confirm this.

Table 15. Budesonide DOE1 particle size distribution

| | $D_{10}$ | $D_{50}$ | $D_{90}$ | Span |
|---|---|---|---|---|
| Point2 | 0.79 | 1.3 | 2.1 | 1 |
| Point4 | 0.48 | 1.2 | 2.9 | 2 |
| Point5 | 0.79 | 1.5 | 2.6 | 1.2 |
| Point7 | 0.64 | 1.6 | 43.2 | 26.6 |
| CP1 | 0.77 | 1.4 | 2.3 | 1.1 |
| CP2 | 0.79 | 1.4 | 2.3 | 1.1 |

### 8.6.3 Crystallinity

The XRPD diffractogram of the budesonide DOE1 products are presented in Figure 34. The pattern of each produced batch resembles closely the crystalline pattern of the raw material (Fig. 21, crystalline budesonide). The differences in the peak heights may be a sign of amorphous content in the spray dried batches (Fix and Steffens 2004; Grisedale *et al.* 2011).

From Figure 34 it can be observed that the lowest peaks were in the batches Point2 and Point 4 and the highest peaks were in the batches Point 7 and CP 2. The high peaks in point 7 could partly be the result of larger observed particle size (table 15) (Grisedale *et al.* 2011), although this claim is not supported by the particle size results for CP2 (table 15). Both the lowest batches had the lowest ethanol concentration and lowest solid content when compared with the others. This may be explained by the fact that ethanol concentration and low solids concentration have both been indicated as variables that could alter the crystal development (Stieger and Liebenberg 2012) in a rapid process like spray drying (Masters 2002).

The solid state properties dependency on the inlet temperature used in spray drying (Mezzena *et al.* 2009) is challenged by the results from point 4 and point 2 that had similar results but different inlet temperatures (Table 4). No other polymorphs seem to be present in these batches (Velaga *et al.* 2002; Steckel *et al.* 2004; Kubavat *et al.* 2012).

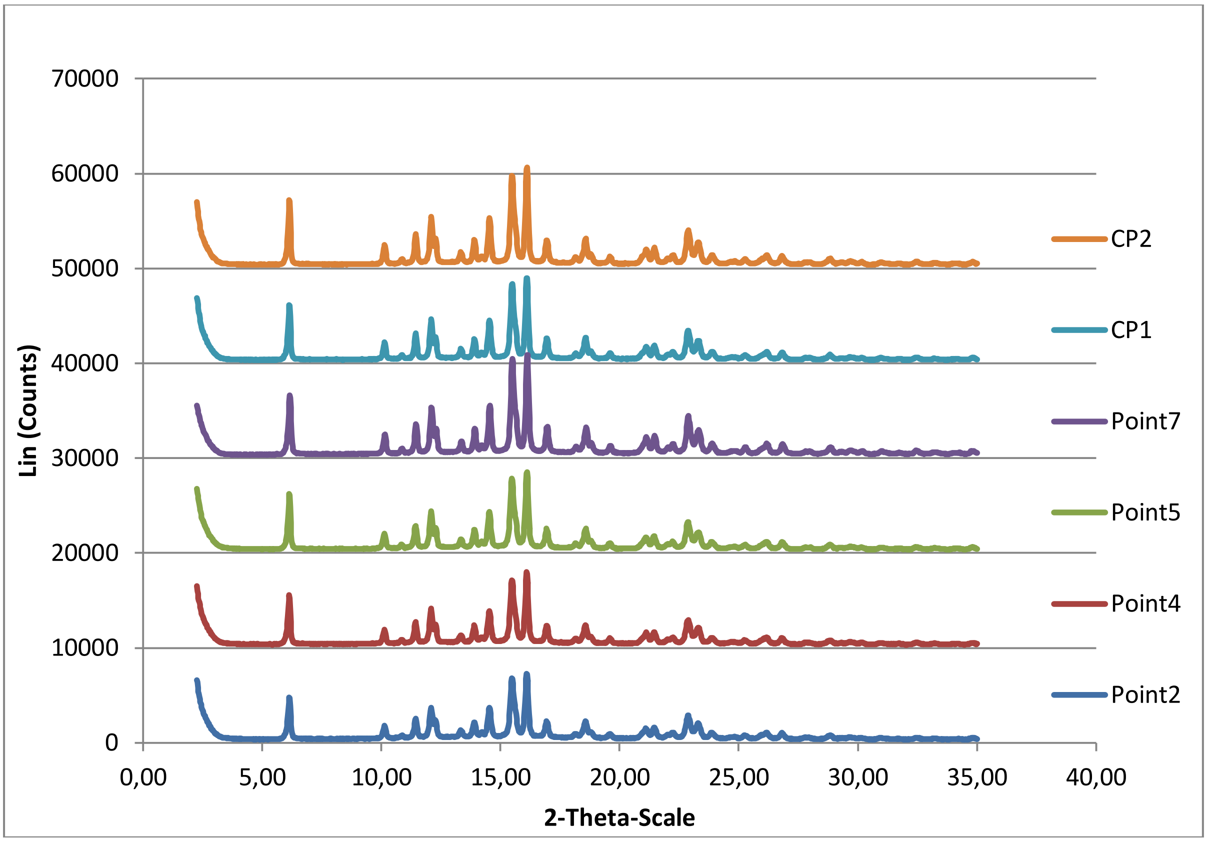


Figure 34. XRPD diffractograms of budesonide DOE1 batches.

The seemingly crystalline nature of the spray dried budesonide (Fig. 34) is not in line with the studies conducted by Nolan *et al.* (2009) who produced amorphous budesonide with a spray dryer under similar conditions. This is somewhat surprising considering the differences between their non-porous budesonide particle production (Nolan *et al.* 2009) and the produced point 5 (Table 4). The main differences noted are the nozzle cooling system, different budesonide concentration, different raw material quality and different feed speed. However, there is some evidence that most of these differences might increase crystallinity.

The nozzle cooling system will lower the temperature of the feed and thus lower the solubility of budesonide (Mota *et al.* 2009) and increase crystallization (Stieger and Liebenberg 2012). To combine the lowering of temperature with higher budesonide concentration even increases the crystallization tendency. The slower solubility of larger raw material might have left some unsolved material into the solution that had acted as seeds for crystallization (Stieger and Liebenberg 2012). Unlike the others, the slower feeding might have decreased the crystallinity by shortening the drying period (Masters 2002). The combined effect of these parameters is challenging to define due to the interactions between different parameters that only emphasize the complexity of the spray drying process (Amaro *et al.* 2011).

### 8.6.4 Morphology

The individual spray dried budesonide particles from DOE1 seem to be round and apparently loosely aggregated together (Fig. 35) judging from the figure and from the particle size distribution data. These types of loosely aggregated small round particles might be beneficial in the DPI (Newman *et al.* 2009).

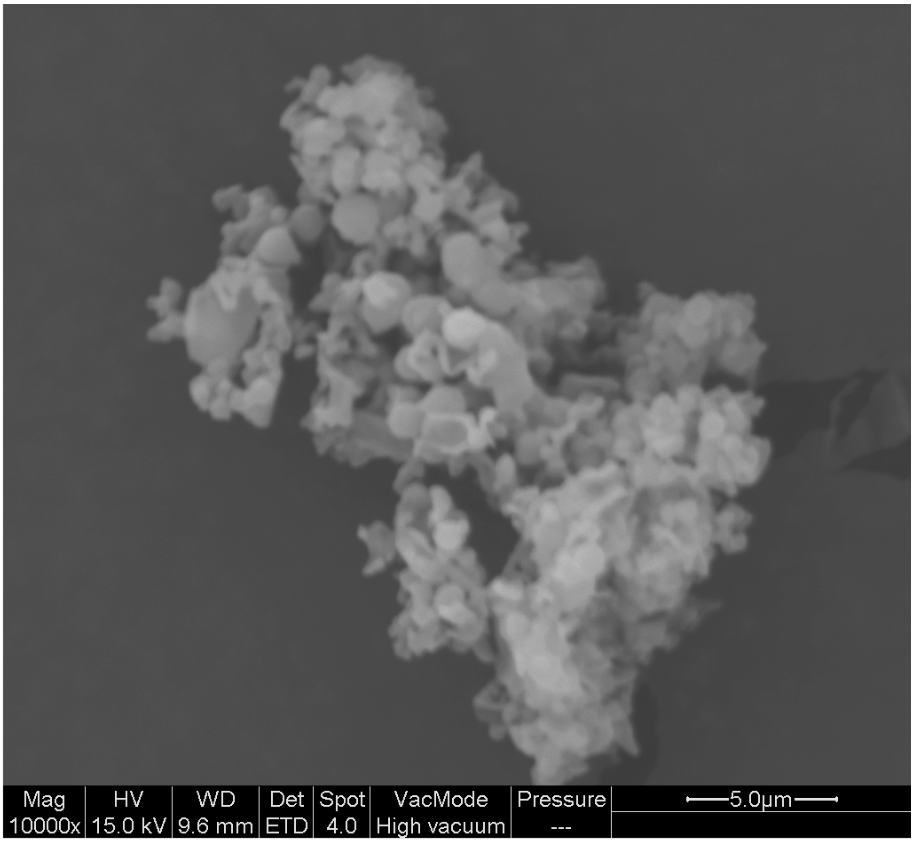


Figure 35. SEM pictures of spray dried budesonide from DOE1 (point 4, Table 4)

## 8.7 Further studies on budesonide

### 8.7.1 Yield

From the yields of the further studies (Table 16) it is clearly noted that the lowering of the spray gas flow (rotameter value) increases the yield. This is, interestingly, exactly an opposite result when comparing with literature (Goula *et al.* 2005; Amaro *et al.* 2011). These results might be caused by the increase in spray droplet size (Masters 2002). This larger droplet would have more material in it and therefore it would dry to larger particles. These larger particles are more efficiently captured in the cyclone which is ineffective in capturing the smallest size fractions.

Table 16. Budesonide further studies yields

| | Yield (g) | Yield (%) |
|---|---|---|
| Test1 | 4.1 | 41 |
| Test2 | 3.1 | 31 |
| Test3 | 2.2 | 22 |
| Test4 | 8.4 | 82 |
| Test5 | 2.1 | 21 |

### 8.7.2 Particle size distribution

From the particle size data (Table 17) it is clearly noted that Test 4 result are slightly different from others. All the experiments are mainly within the inhalable range (1-5 μm). The poor yields in Test 1-3 and the observed blocking of the bag filter might have altered the results for the finer fractions.

Table 17. Budesonide further testing particle size distribution

| | $D_{10}$ | $D_{50}$ | $D_{90}$ | Span |
|---|---|---|---|---|
| Test1 | 0.82 | 1.4 | 2.4 | 1.1 |
| Test2 | 0.72 | 1.3 | 2.1 | 1.1 |
| Test3 | 0.76 | 1.3 | 2.1 | 1 |
| Test4 | 0.55 | 2.2 | 5.1 | 2.1 |

### 8.7.3 Crystallinity

The crystalline form was similar in all four batches, (Fig. 36 and 37). However, some differences in the peak heights were noted. Previous studies have shown that higher peaks could be an indication of higher crystallinity (Fix and Steffens 2004; Grisedale *et al.* 2011) or larger particle size (Grisedale *et al.* 2011). This is particularly interesting for different samples in Test5 (Fig. 37) as it seems that material that has not adhered to the walls of the sample container might be more crystalline. According to this the harvesting place from spray dryer could affect the solid state form of the product. The experiments conducted by Islam and Langrish (2010) support these findings by suggesting that the wall deposition in the spray dryer could affect the solid state of the product but not necessarily the level of crystallinity.

There is also evidence that a major part of crystallization could in some cases take place in the walls of the spray dryer (Islam and Langrish 2009).

The usage of different drying and spraying gases could have explained this crystallinity as Nolan *et al.* (2009) used atmospheric air to create amorphous budesonide and in this study crystalline budesonide was dried with nitrogen. The effects of different gas types in spray drying is supported by Islam *et al.* (2010b) and Bianco *et al.* (2012), but the results obtained by Mezzena *et al.* (2009) strongly challenge this effect. In addition the purity and solvent vapour content of the new and recycled gases remain largely uncharted (Bianco *et al.* 2012). Solvent vapour traces could alter the solubily of substances and powder traces could act as nucleation centers contributing to crystallization (Stieger and Liebenberg, 2012).

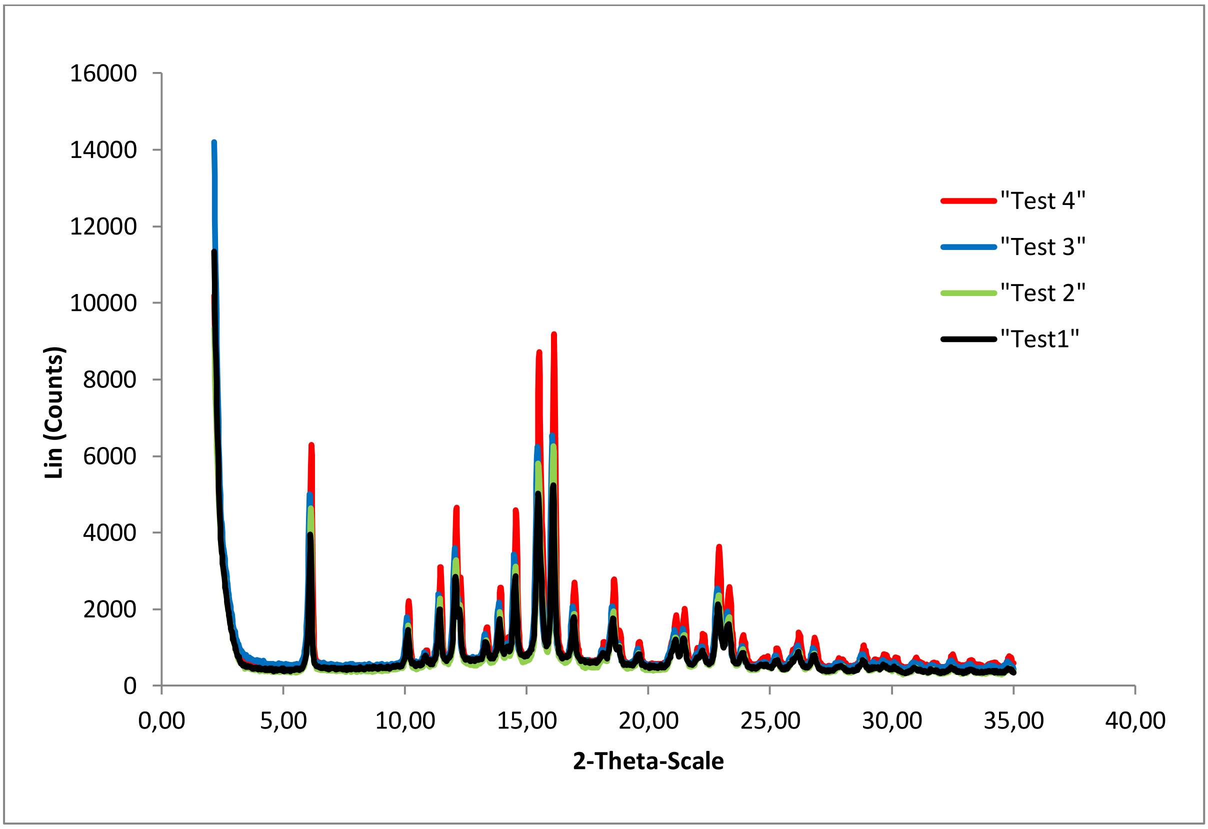


Figure 36. XRPD diffractograms of further budesonide testing points 1-4.

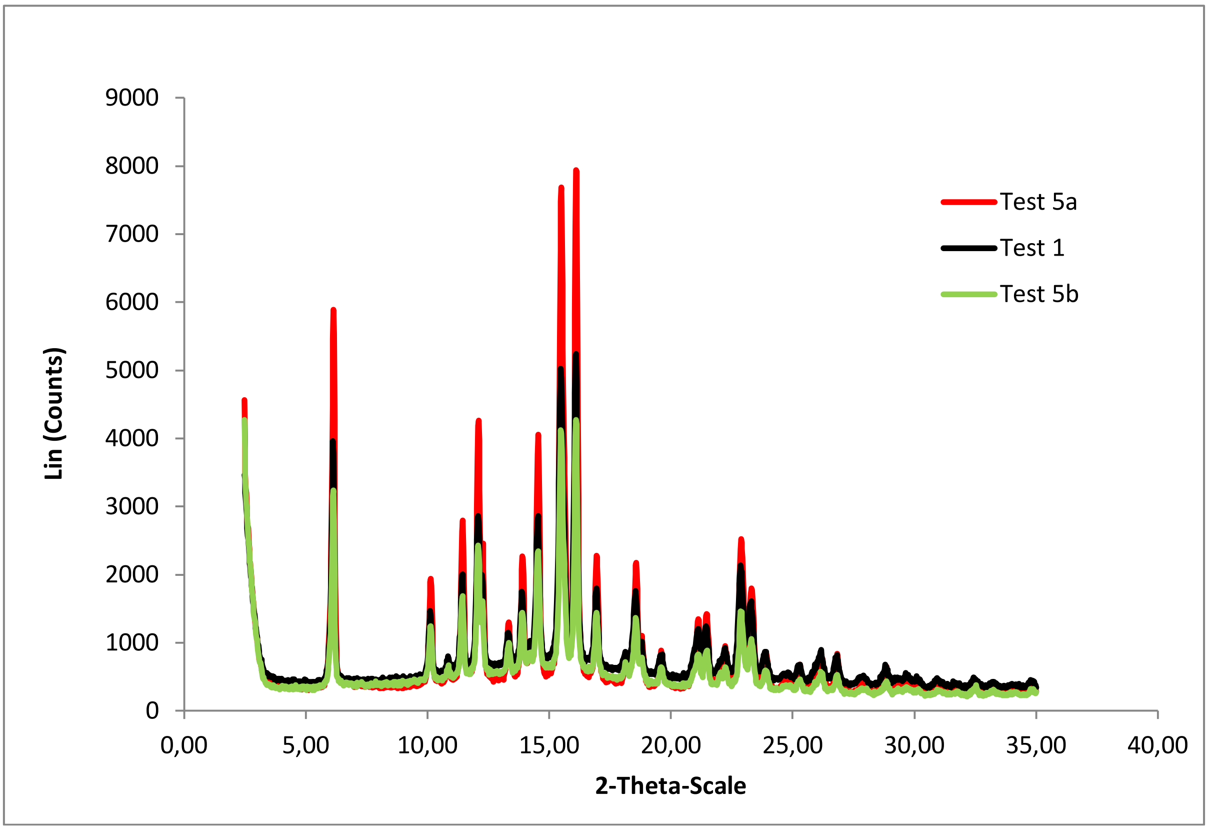


Figure 37. XRPD diffractograms of further budesonide testing point 5. Test 5a and 5b represent samples that have been collected with different means. Test 5a was poured to the sample container from the spray dryer's product vessel and the Test 5b was the remaining material that had to be scratched out from there.

### 8.7.4 Morphology

The SEM pictures from the test batches 1-4 (Fig. 38) indicate that the particles are round and to some extent aggregated to each other. These pictures seem to support the laser diffractometer results that the particle size is within the inhalable range (1-5 µm). The finding that the test 4 batch is larger sized than the three others is also supported by Figure 38. This could also be the reason for higher peaks in Figure 36 (Grisedale *et al.* 2011).

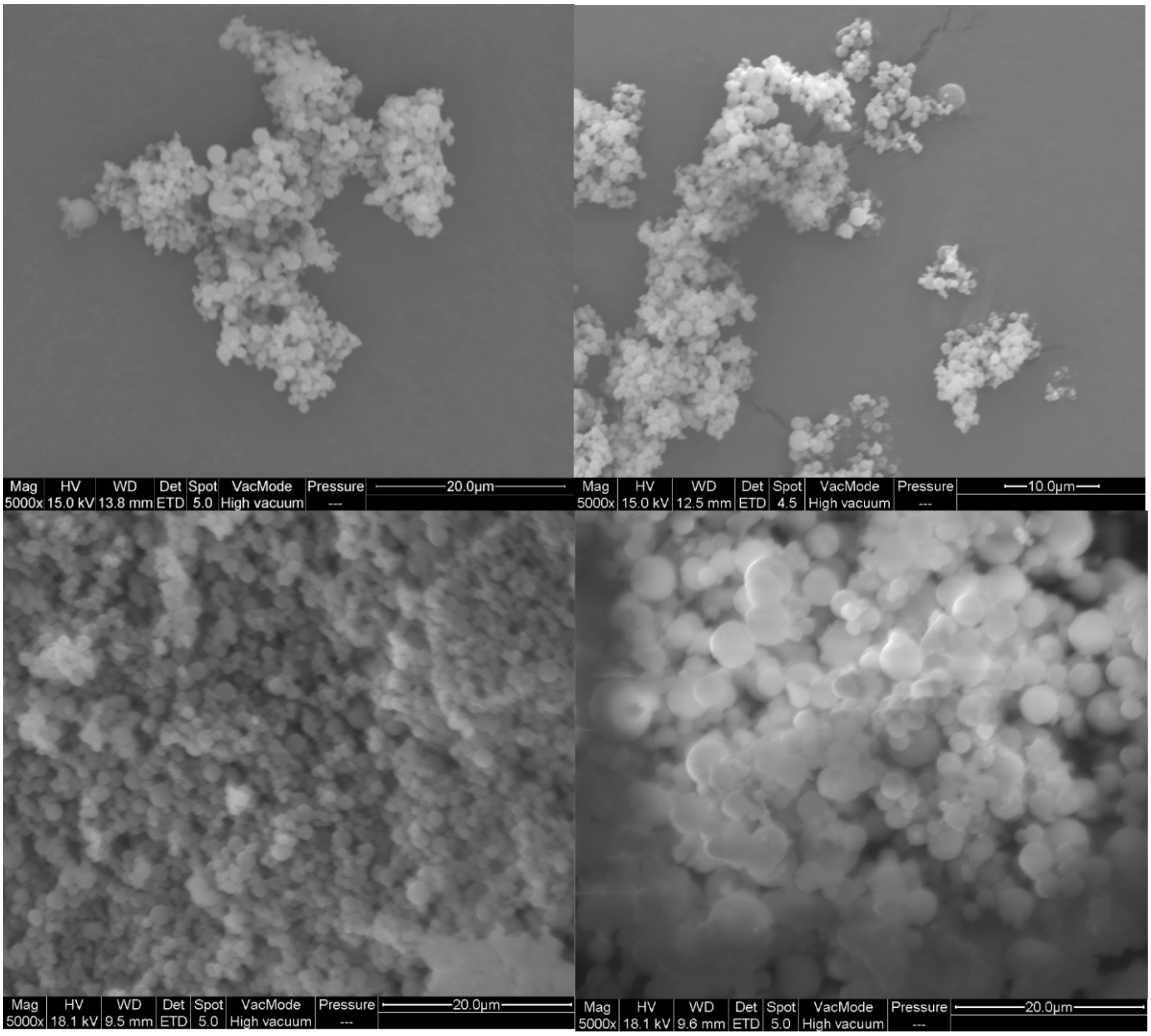


Figure 38. SEM pictures of the budesonide test Batches 1-4. Upper left corner Test 1, Upper right corner Test 2, lower left corner Test 3 and lower right corner Test 4.

## 8.8 Annealing of budesonide

From Figure 39 and 40 it can be seen that the peaks have elevated and that the valleys have become deeper. A small elevation of peaks can also be seen for the controlling material (data not shown). According to the research done by Fix and Steffens (2004) and Grisedale *et al.* (2011) this may indicate an increase in crystallinity or in particle size (Grisedale *et al.* 2011). A small difference is also seen between the micronized and unmicronized controlling samples (data not shown) indicating possibly the production of amorphous material in micronization process.

A difference can also be observed in the speed of crystallization when comparing Figure 39 and 40. The higher ethanol activity has fully crystallized the sample in 4th day measurement, whereas in the lower ethanol activity the process has continued till the 16th day measurement. These differences indicate that higher ethanol activities increase the speed of the process.

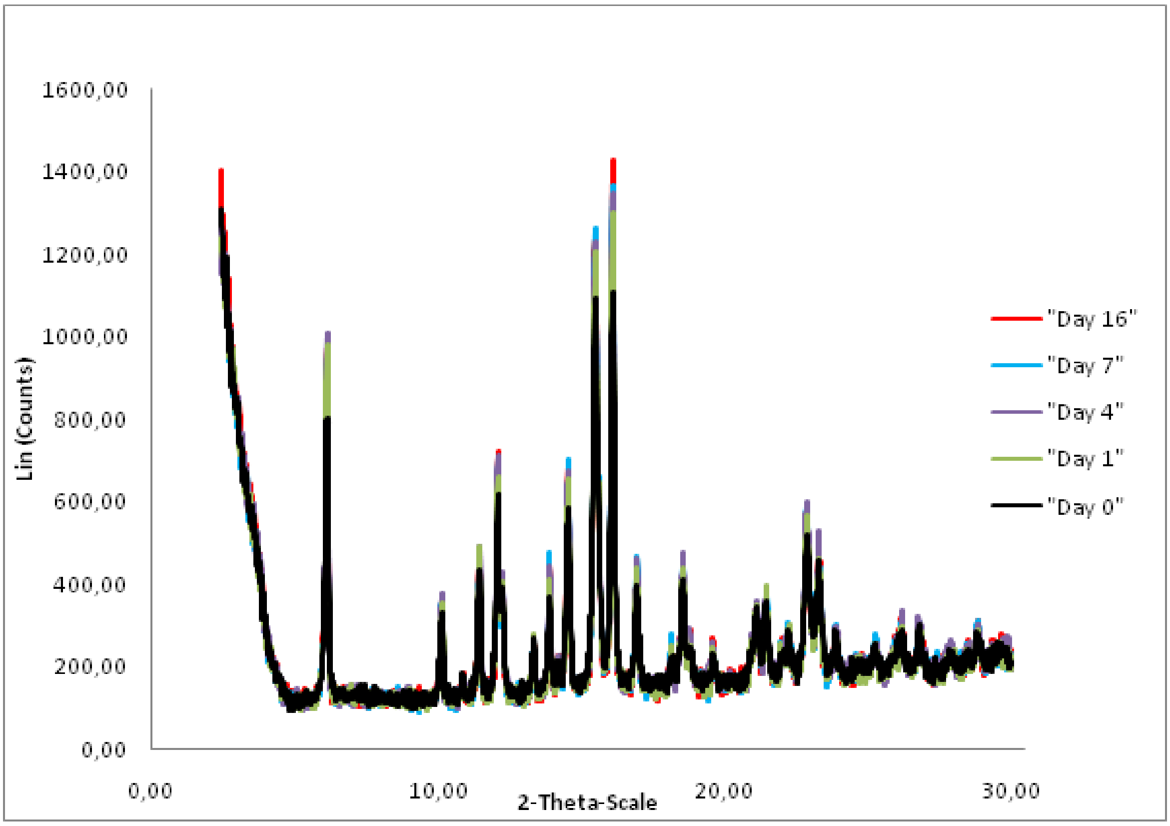


Figure 39. XRPD diffractograms of Test 3 budesonide batch annealed in 74% ethanol activity.

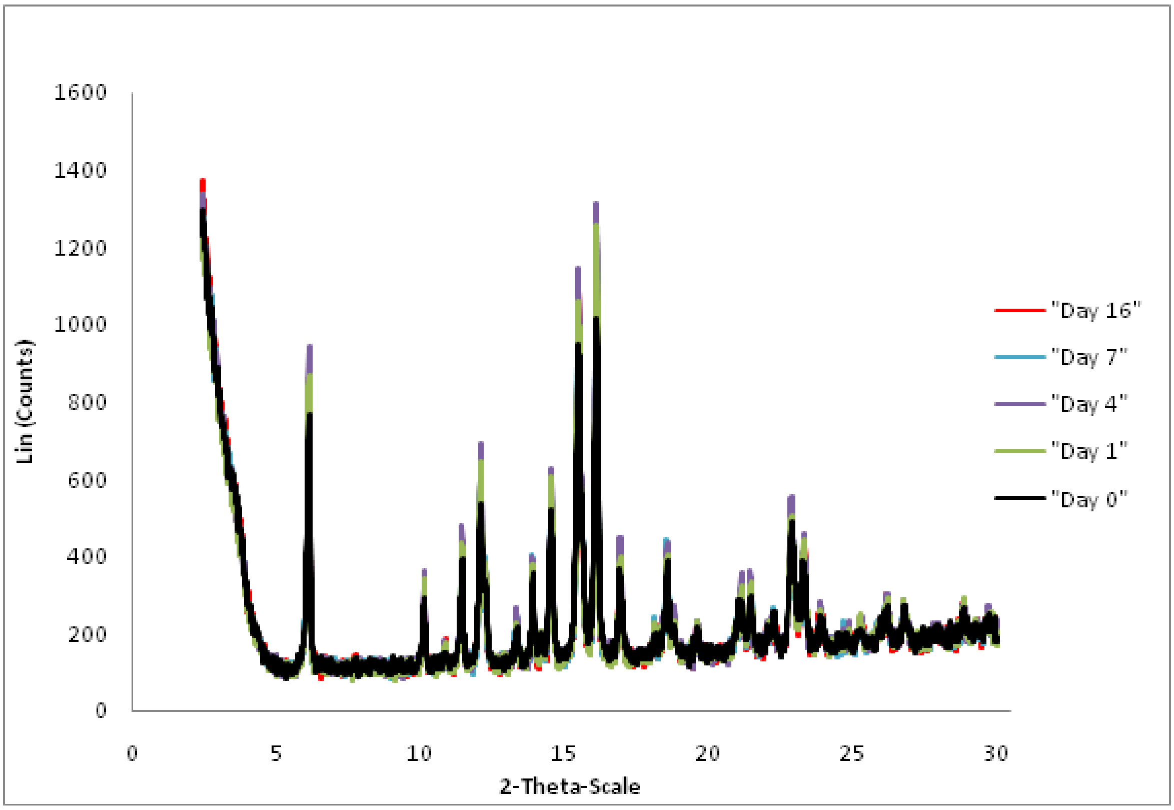


Figure 40. XRPD diffractograms of Test3 budesonide batch annealed in 100% ethanol activity.

From the annealing results for Batch Test3 it can be concluded that this spray dried batch altered in annealing process. This can be observed from the altered X-ray diffractograms (Fig. 39 and Fig 40). The change in annealing process is mostly a combination of increased crystallinity and increased particle size as observed by Brodka-Pfeiffer *et al* (2003). Unfortunately the current setup does not allow monitoring of the particle growth. The conclusion is that the spray-dried material was not totally crystalline during the first X-ray measurements. Further studies need to be conducted in order to define the relative contribution of particle size growth and increase in crystalline material to the results respectively.

# 9 CONCLUSIONS

Both model substances were successfully spray dried. Spray dried salbutamol sulphate turned out to be amorphous and budesonide turned out to be crystalline. Both products were within the inhalable size range (1-5 µm). The yields varied a lot due to the apparent dependencies on process parameters and material properties. The use of very small batch sizes should be avoided to maximize yield percentage and to provide more usable material for analysis.

The effects of the solid concentration on the product quality seem to be limited on the increased yield, particle size and partly on increased crystallinity. The increased crystallinity is due to the solubility exceeding solid content and the formation of suspension. This is confirmed by the usage of nozzle cooling system that prevents the heating up of the solution and therein prevents an increase in solubility in the nozzle. The effects on particle size are somewhat mixed but the trend is that an increase in concentration of solids will increase particle size. An increase in the concentration of solid substances increased the yield notably. An increase in inlet temperature may increase particle size and decrease surface roughness but seems not to affect the level of crystallization. Particles with high surface roughness could potentially be beneficial due to their aerodynamic properties if the process could be properly controlled. The effects of the used ethanol/water ratios were mostly on yield due to the solubility changes for the test substances. The increased solubility on the used solvent mixtures increased yields when saturated solutions were used. The used ethanol/water ratios seemed to have no effect on the solid state of the products. Of the other tested variables (Spray air flow, raw material quality and the addition of additives) only spray air flow seemed notably to affect the product within the variable ranges used. A decrease in spray air flow seemed to increase yield and particle size. This may be due to more efficient capturing of the larger particles in the cyclone.

The somewhat mixed results in the effects of the used variables are partly due to dependency of the results on the nature of different substances and partly due to the interactions between different variables. These things cause the spray drying process to be a versatile method that requires careful design of experiments.

Spray dried amorphous salbutamol sulphate was successfully annealed into a crystalline material and partly crystalline budesonide was annealed to a possibly more crystalline state. The kinetics of the annealing procedure still remains largely unexplored as well as the factors associated with it. The problematic size growth associated with annealing was noticed in part of the batches. Due to the sample preparation and measurement techniques used the effect of particle growth could not be verified in all samples.

Future studies with spray dryers could be focused on budesonide as it interestingly produced crystalline particles within the inhalable particle size range. The dependency of the solid state of spray dried budesonide on the used spraying and drying gases could be studied more closely. In addition the dependency of the surface roughness on temperature of the spray dried salbutamol sulphate particles should be studied more. They could also be tested in an inhalator. In annealing the dependency of particle size growth in Fluxus on humidity and temperature should be studied more closely.

# 10 ACKNOWLEDGEMENTS

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