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Controlling Polymorphism of Carbamazepine Nanoparticles in a Continuous Supercritical CO$_2$-Assisted Spray Drying Process

*Barry Long, Gavin M. Walker, Kevin M. Ryan, Luis Padrela*

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Abstract

Controlling polymorphism in the transition from batch to continuous crystallization represents a major obstacle for the pharmaceutical industry. This work demonstrates a novel methodology to control the polymorphism of carbamazepine (CBZ) nanoparticles, a highly polymorphic BCS class II drug, using a continuous supercritical CO$_2$ antisolvent-assisted nano spray drying (SASD) process. We show herein that when supersaturation conditions are achieved in the high-pressure SASD nozzle in the presence of anionic additives (e.g. sodium stearate, sodium dodecyl sulfate), nanoparticles of the metastable CBZ form II (using sodium stearate) or the stable CBZ form III (using sodium dodecyl sulfate) are obtained from methanol solutions, respectively. This novel methodology provides control over the final polymorphic form of CBZ obtained by (1) templating the desired polymorphic form when supercritical CO$_2$ supersaturates the CBZ-additive methanol solution in the nozzle and (2) avoiding/minimizing the occurrence of any possible polymorphic transformation by immediately spray drying the supercritical antisolvent induced suspension into a dried fine powder. These results contrast with those obtained when using non-supersaturating conditions in the SASD nozzle (amorphous CBZ is obtained, regardless of the additive used) and when using conventional spray drying (SD) where there is no antisolvent effect in the nozzle (CBZ form IV is obtained, regardless of the additive used). The impact that the mass ratio of methanol and supercritical CO$_2$ has on the supersaturation and consequently on the polymorphic outcome of carbamazepine obtained from batch and continuous supercritical CO$_2$ antisolvent crystallization processes is also discussed.
Keywords
Continuous manufacturing, nucleation, crystallization, antisolvent effect, polymorphic control, additives

Introduction
Low bioavailability of drug candidates due to poor water solubility accounts for one of the greatest obstacles facing the pharmaceutical industry. Poorly soluble compounds represent 40% of the top 200 oral drugs marketed in the US and 90% of new chemical entities, highlighting the importance of establishing a comprehensive method to increase the bioavailability of these compounds.\(^1\)\(^2\)

Carbamazepine (CBZ) is an antiepileptic BCS Class II drug, meaning that it has high intestinal permeability but poor water solubility resulting in reduced bioavailability.\(^3\) CBZ is a suitable Active Pharmaceutical Ingredient (API) model candidate to study polymorphism in crystallization processes as it exists in at least four anhydrous polymorphs, with form III being the most thermodynamically stable form at room temperature.\(^4\)\(^5\) Two popular approaches that have been successfully used to improve the bioavailability of drugs are (1) generating amorphous or metastable forms of the drug and (2) reducing the particle size.\(^6\)\(^9\)

Polymorphism is a phenomenon that can affect any pharmaceutical drug and is the ability of a solid compound to exist in more than one crystalline form. It is estimated that more than 50% of active pharmaceutical ingredients have more than one polymorphic form.\(^10\)\(^11\) Isolating pure polymorphic forms has proven to be a challenging task, despite many different techniques employed to achieve this.\(^12\)\(^14\) Impurities, in the form of various other polymorphic forms, is one of the most common obstacles that the pharmaceutical industry faces during the manufacture of an API.\(^15\)\(^17\) Although continuous crystallization boasts higher levels of control over some process variables when compared to batch processes, robust approaches to control
Polymorphism during continuous crystallization has yet to be comprehensively achieved. Only recently have researchers attempted to address the complexity of controlling polymorphism in continuous crystallization processes.\textsuperscript{18-20} As a result of this, the pharmaceutical industry have placed their focus on polymorphic studies to avoid adverse effects such as spontaneous conversion between different crystalline phases and to take advantage of beneficial effects such as improved physicochemical properties and patent life extensions.\textsuperscript{15, 21-22} Polymorphism can result in differences in physicochemical properties leading to differences in solubility, dissolution rate and bioavailability which are critical parameters for the pharmaceutical industry.\textsuperscript{23-24} Polymorphism can be affected by various processing conditions in pharmaceutical crystallization such as the type of crystallization mode used (batch versus continuous), solvent, temperature, antisolvent, and the use of additives or surfactants.\textsuperscript{18, 25-30} The use of additives to control polymorphism has been explored by many researchers in an attempt to isolate pure forms of both stable and metastable polymorphs of various compounds.\textsuperscript{26, 31-35} Davey \textit{et al.} have studied the effect of additives on generating and isolating metastable polymorphs for various compounds.\textsuperscript{32-33} In many cases when additives are selected for this purpose, they have been shown to incorporate themselves stereoselectively into the growing faces of the crystals, thereby inhibiting further growth of these faces and promoting alternative polymorphic forms.\textsuperscript{32-33, 36-37} Another technique that may also be utilized to control the polymorphism of different compounds includes the confinement of crystallization habitats.\textsuperscript{38-39} It has been reported that the size constraint imposed by nano- and submicron- scale pores during crystallization can influence the final polymorphic form obtained.\textsuperscript{39-41} The confinement can cause the relative free-energy values for various polymorphs to become almost equivalent, thereby reducing the preference for one polymorphic form to crystallize over another.\textsuperscript{40-42} This paper reports on the transition of a supercritical antisolvent crystallization process from batch to continuous, a development trend that is encouraged by most regulatory bodies for
pharmaceutical manufacturing processes.\textsuperscript{43-44} Currently, pharmaceutical companies are reluctant to make the switch as designing a continuous manufacturing process typically requires a higher level of process control and monitorization than batch manufacturing processes in addition to further investment in plant.\textsuperscript{44-46} Scaling up represents itself as one of the major obstacles that limits pharmaceutical processing due to difficulties arising from the prediction of lab-scale to industrial-scale evolutions.\textsuperscript{45} One of the selling points for continuous manufacturing is that the requirement for scaling up is removed as emphasis is shifted to scaling down instead. Evidence shows that making the switch could prove worthwhile in the long term as continuous manufacturing provides:\textsuperscript{47-48}

- Fewer steps in the process, resulting in faster production times.
- Lower costs.
- Real time in-line monitoring of experimental runs using quality-by-design approaches.
- Possibility of scaling-down instead of scaling-up.

Continuous processing features heavily in most fields of research as it is expected that these techniques will dominate the first choice crystallization mode for the pharmaceutical industry. Pharmaceutical techniques such as plug flow crystallization, milling, high-pressure homogenization and antisolvent methods have recently become a popular and effective technique to control particle size, shape and polymorphic form of APIs.\textsuperscript{49-53} Supercritical fluid (SCF) technologies have also emerged as techniques which can be employed in batch, semi-continuous and more recently in continuous mode (in spray drying methods which use CO\textsubscript{2} as the atomizing fluid), to generate unique polymorphic forms of APIs which are not reproducible by other techniques.\textsuperscript{54} Supercritical fluid methods provide benefits over conventional precipitation methods in regards to generating high levels of supersaturation, polymorphic control, particle size control, low residual, as well as providing low levels of residual solvent.
in the final product.\textsuperscript{55-59} Carbon dioxide is the most commonly used SCF as it is non-toxic, inexpensive and has the ability to act as an antisolvent.\textsuperscript{26, 59} Another reason for the popularity of carbon dioxide as a supercritical fluid is due to its low critical temperature and relatively low critical pressure ($T_c = 31.1^\circ\text{C}$, $P_c = 7.38$ MPa).\textsuperscript{59-60} This low temperature allows manufacturers to process thermally sensitive pharmaceutical compounds using this SCF. Supercritical CO$_2$ has a low viscosity and a high diffusivity coefficient making it a viable candidate for antisolvent processing.\textsuperscript{59, 61} An additional benefit of using supercritical CO$_2$ as an antisolvent is that there is less risk of a hydrate forming during processing as would be a concern when using water, a common antisolvent in pharmaceutical crystallization.\textsuperscript{62}

Although supercritical fluid techniques can utilize supercritical CO$_2$ in three different roles (as a solvent, antisolvent or atomization enhancer), this work presented herein utilizes supercritical CO$_2$ as both an antisolvent and atomization enhancer. In our supercritical CO$_2$ antisolvent-assisted nano spray drying method (SASD) presented herein, supercritical CO$_2$ mixes with the solution containing the drug and additives in a small volume high pressure co-axial nozzle. Supersaturation is induced in the nozzle and nucleation follows. Unlike other processes such as the gas antisolvent (GAS) crystallization process, atomization is involved in the SASD method which results in the generation of a spray of ultra-fine droplets in which the solvent is removed by thermal means. This process is an attractive method for the pharmaceutical industry as it can be easily adapted to existing conventional spray dryers. As the region of high pressure is concentrated to the small volume mixing chamber (nozzle), there is little requirement for specialist high-pressure equipment.

Padrela \textit{et al.} demonstrated that the use of additives provides control over the molecular packing of carbamazepine (CBZ) molecules at the pre-nucleation stage in a batch supercritical antisolvent process, resulting in the production of specific polymorphic forms of CBZ.\textsuperscript{26} These authors used density functional theory modeling to predict that nonpolar parts of CBZ
molecules interact with the nonpolar tails of the anionic additive, sodium stearate (SS), resulting in the templating of empty columnar channels which SS can interact with for the generation of CBZ form II. The absence of these channels is observed when sodium dodecyl sulfate is selected, which causes templating of CBZ to represent form III. The objective of the work presented herein is to investigate if this effect can be replicated in a continuous SASD process, as the kinetics and mechanisms for crystallization in each of these processes (batch versus continuous) are expected to be different. Supercritical CO$_2$ nano spray drying and related supercritical antisolvent methods typically promote the formation of metastable crystalline forms of APIs due to their fast crystallization and drying steps. However, our novel methodology presented herein uses molecular additives in an SASD process to enable control over the final API polymorphic form generated (exemplified herein for carbamazepine as our model system). This approach consists of continuously templating the desired polymorphic form of CBZ in the nozzle (where supercritical CO$_2$ antisolvent mixes with the solution containing the drug and the additive) by using specific additives before crystallization takes place (which will mostly occur after the nozzle exit during the spray drying step).

In this work a supercritical antisolvent method, which was demonstrated elsewhere for the production of distinct polymorphic forms of CBZ microparticles, is converted into a continuous SASD method for the production of distinct polymorphic forms of CBZ nanoparticles. A Design of Experiments (DoE) methodology was applied to study the influence of selected process parameters (e.g. solution feed rate, % of additive) on the polymorphic outcome of CBZ produced by the supercritical CO$_2$ antisolvent nano spray drying method (SASD). The mass ratio of supercritical CO$_2$ and methanol required to achieve supersaturation and consequently precipitation of CBZ was determined using a batch supercritical antisolvent method, and this information was used to select the required processing conditions in SASD to ensure that supersaturation is achieved. This paper also aims to clarify if the influence of
additives on the polymorphism of CBZ is only caused by the antisolvent effect of CO₂ in the SASD nozzle or if it can also be achieved using lower supersaturation levels or drying rate in conventional spray drying.

**Experimental Section**

*Materials*

Carbamazepine (form III) was purchased from Kemprotex. Maltitol, sodium stearate (SS), ethyl cellulose, sodium dodecyl sulfate (SDS), sodium deoxycholate and pluronic F-127 were purchased from Sigma Aldrich and used without further purification (purity was >99.9%). Eudragit L-100-55 was a gift from Evonik Industries. Carbon dioxide (99.98%) was supplied by BOC (Ireland). Table 1 summarizes the different types of additives used in this work. These additives were selected from a manuscript previously reported by Padrela et al. where they were shown to favor the formation of either pure forms II or III of carbamazepine in a batch supercritical antisolvent method.

<table>
<thead>
<tr>
<th>Anionic Surfactants</th>
<th>Non-ionic surfactants</th>
<th>Anionic polymers</th>
<th>Non-ionic polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium stearate</td>
<td>Maltitol</td>
<td>Eudragit L-100-55</td>
<td>Ethyl cellulose</td>
</tr>
<tr>
<td>Sodium dodecyl sulfate</td>
<td>Pluronic F-127</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sodium deoxycholate</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Solution Preparation*

For the precipitation experiments of carbamazepine (CBZ) using a batch supercritical
antisolvent process, 50 mg of Carbamazepine (CBZ) was dissolved in 1 ml of methanol and placed in an ultrasonic bath until the solids were completely dissolved (~5 minutes). For the production of carbamazepine nanoparticles using a supercritical CO$_2$ antisolvent-assisted nano spray drying (SASD) process, CBZ with/without additives was dissolved in 20 ml of methanol (50.0 mg/ml) and placed in an ultrasonic bath for a similar period of time as mentioned above. When using additives for the preparation of CBZ solutions in methanol, 5% w/w (2.5 mg/ml) of each additive was dissolved in the CBZ solutions. When low concentration experimental runs (SASD 20, 21 and 22) were completed, the concentration of CBZ was reduced to 17.0 mg/ml and 5% w/w of specific additives (0.8 mg/ml) were added. The solutions were then filtered through a 0.2µm pore size nylon filter (Whatman Inc., Florham Park, NJ) to remove any undissolved material.

_Precipitation of Carbamazepine in a batch supercritical antisolvent process_

In order to determine the pressures and the mass ratios of solution to supercritical CO$_2$ at which supersaturation would occur in the SASD nozzle, precipitation of CBZ was performed using a batch supercritical antisolvent process. This apparatus consisted of a 10 cm$^3$ stainless steel high-pressure vessel shown in Fig. 1 and as described elsewhere.$^{26}$ The pressure was determined using a pressure transducer (Omega model PX603). A high-pressure stainless steel storage vessel was used to store the CO$_2$ to allow it to reach the set temperature inside a temperature-controlled (monitored by a T-type thermocouple) air chamber. A solution containing 50 mg of CBZ dissolved in 1 ml of methanol was placed inside the high-pressure vessel and compressed with CO$_2$ at a rate of 1 MPa/minute. During the addition of CO$_2$, the solution was subjected to magnet stirring at 600 rpm to facilitate homogeneity. Once precipitation was visually observed through the borosilicate window, the value was recorded (Table 6) and the vessel was depressurized. This value was determined to be the antisolvent
crystallization point. Although this methodology does not consider that the batch and continuous processes are kinetically different, it provides an indication on the pressure and mass ratio of supercritical CO$_2$ to methanol at which supersaturation should occur in the SASD high-pressure nozzle. Each solubility experiment was performed at least three times to ensure repeatability.

![Diagram of the batch supercritical antisolvent apparatus.](image)

**Figure 1.** Schematic diagram of the batch supercritical antisolvent apparatus used for solubility testing. 1, CO$_2$ cylinder; 2, gas compressor; 3, temperature controlled air chamber; 4, stainless steel storage cylinder; 5, magnetic stirrer plate; 6, high-pressure vessel; 7, exit valve; PIC: pressure controller; TC: temperature controller.

*Supercritical CO$_2$ Antisolvent-Assisted Nano Spray Drying (SASD)*

Figure 2 shows a schematic of the SASD apparatus. The primary spray drying apparatus consists of three main zones that are representative of the supercritical antisolvent nano spray drying process (SASD). The first zone is the high-pressure small-volume stainless steel nozzle (number 5 in Fig. 2), where both mixing of CO$_2$ with the CBZ solution, and supersaturation/antisolvent nucleation occur. The mixing volume for this section is 0.1 cm$^3$. The second zone is the drying chamber which is a 1000 cm$^3$ vessel (number 6 in Fig. 2) surrounded by a temperature controlled water jacket which facilitates the drying of the solvent.
once atomized. The final zone is the particle collector, which consists of a metal filter (number 7 in Fig. 2) and filter nylon paper with 0.2 µm pore size.

During an SASD experiment, CO$_2$ was compressed using a Teledyne ISCO 260D pump. The pressure and temperature were controlled as described above. The nozzle was maintained at 50°C by using heating resistors in close proximity to the nozzle. The CBZ methanol solution was pumped by a Waters 515 HPLC pump to the high-pressure SASD nozzle where it mixed with the supercritical CO$_2$. After the solution was passed through the nozzle, the CO$_2$ was depressurized and any residual solvent was evaporated during the spray drying step. The samples were harvested and stored in a desiccator prior to characterization to prevent exposure to humidity which could result in polymorphic conversions over time.

Three control SASD experiments were performed at different solution flow rates (0.10, 0.25 and 0.40 ml/min) to identify the polymorphic form of CBZ obtained by the SASD method in the absence of additives (Table 2). The pressure selected for these experiments was 12.0 MPa (which corresponded to a solution to SCF ratio of 0.005-0.021) as it was determined to be sufficient for antisolvent crystallization (a solution to SCF mass ratio of 0.5 was determined to be the maximum value allowable using a batch supercritical antisolvent method) to occur. Upon completion of these experiments, several additives (selected from the work reported by Padrela et al.$^{26}$) were added to the CBZ methanol solutions and processed using the SASD method, as reported in Table 3. The pressure selected for these experiments was 17.0 MPa (solution to SCF ratio of 0.011) which was sufficiently over the pressure required for antisolvent crystallization to occur.

Table 2. List of Carbamazepine (CBZ) Solid Forms Obtained at Different Solution Flow Rates Without the Use of Additives Using Supercritical CO$_2$ Antisolvent-Assisted Nano Spray Drying (SASD) $^a$

<table>
<thead>
<tr>
<th>Sample Reference</th>
<th>$F_{\text{Solution}}$ (ml/min)</th>
<th>$F_{\text{Solution}}$ (g/min)</th>
<th>$R_{\text{Flow Ratio}}$ Solution/SCF</th>
<th>Solid Form Obtained</th>
</tr>
</thead>
</table>

$^a$
<table>
<thead>
<tr>
<th></th>
<th>SASD 1</th>
<th>SASD 2</th>
<th>SASD 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.10</td>
<td>0.25</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>0.079</td>
<td>0.198</td>
<td>0.316</td>
</tr>
<tr>
<td></td>
<td>0.005</td>
<td>0.013</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>I/III</td>
<td>I/III</td>
<td>I/III</td>
</tr>
</tbody>
</table>

For all SASD experiments listed in Table 2, pressure was kept at 12.0 MPa and CO₂ flow rate was kept at approximately 15.0 g/min (30 ml/min). Temperature was 50°C. The concentration of active ingredient (CBZ) was 50 mg/ml in methanol. $F_{\text{Solution}}$: solution flow rate; $R_{\text{Flow Ratio}}$: mass flow-rate ratio of the solution to (CO₂).

Figure 2. Schematic diagram of the continuous SASD apparatus. 1, CO₂ cylinder; 2, gas compressor; 3, CBZ solution flask connected to a HPLC pump; 4, temperature-controlled CO₂ storage cylinder; 5, high-pressure nozzle; 6, drying chamber; 7, filter; 8, Temperature controlled air chamber; TC: temperature controller; PIC: pressure controller.
### Table 3. List of Carbamazepine (CBZ) Solid Forms Obtained Using Supercritical CO\textsubscript{2} Antisolvent-Assisted Nano Spray Drying (SASD) \textsuperscript{b}

<table>
<thead>
<tr>
<th>Sample Reference</th>
<th>Additive</th>
<th>$C_{[CBZ]}$ (mg/ml)</th>
<th>$P$ (MPa)</th>
<th>$R_{Flow Ratio}$ Solution/SCF</th>
<th>Solid Form Obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>SASD 4</td>
<td>No additive</td>
<td>50.0</td>
<td>17.0</td>
<td>0.011</td>
<td>I/III</td>
</tr>
<tr>
<td>SASD 5</td>
<td>Maltitol</td>
<td>50.0</td>
<td>17.0</td>
<td>0.011</td>
<td>I</td>
</tr>
<tr>
<td>SASD 6</td>
<td>Sodium stearate (SS)</td>
<td>50.0</td>
<td>17.0</td>
<td>0.011</td>
<td>II</td>
</tr>
<tr>
<td>SASD 7</td>
<td>Ethyl cellulose</td>
<td>50.0</td>
<td>17.0</td>
<td>0.011</td>
<td>Amorphous</td>
</tr>
<tr>
<td>SASD 8</td>
<td>Sodium dodecyl sulfate (SDS)</td>
<td>50.0</td>
<td>17.0</td>
<td>0.011</td>
<td>I/III</td>
</tr>
<tr>
<td>SASD 9</td>
<td>L-Eudragit 100-55</td>
<td>50.0</td>
<td>17.0</td>
<td>0.011</td>
<td>I</td>
</tr>
<tr>
<td>SASD 10</td>
<td>Pluronic F-127</td>
<td>50.0</td>
<td>17.0</td>
<td>0.011</td>
<td>I and III</td>
</tr>
<tr>
<td>SASD 11</td>
<td>Sodium deoxycholate</td>
<td>50.0</td>
<td>17.0</td>
<td>0.011</td>
<td>I and III</td>
</tr>
<tr>
<td>SASD 20</td>
<td>No additive</td>
<td>17.0</td>
<td>12.0</td>
<td>0.013</td>
<td>Amorphous</td>
</tr>
<tr>
<td>SASD 21</td>
<td>Sodium stearate</td>
<td>17.0</td>
<td>12.0</td>
<td>0.013</td>
<td>Amorphous</td>
</tr>
<tr>
<td>SASD 22</td>
<td>Sodium dodecyl sulfate</td>
<td>17.0</td>
<td>12.0</td>
<td>0.013</td>
<td>Amorphous</td>
</tr>
</tbody>
</table>

\textsuperscript{b}For all SASD additive screening experiments, temperature was 50 °C and solution flow rate was 0.20 g/min (0.25 ml/min). When additives were used, the concentration of each additive in the CBZ solutions was 5% w/w. $P$: pressure inside the high-pressure nozzle; $C_{[CBZ]}$: concentration of carbamazepine (CBZ) in methanol.

**Design of Experiments (DoE)**

When changing the type of additives, as listed in Table 3, 5% w/w of certain additives was determined to be a sufficient amount to produce pure polymorphs of CBZ. Two additives, sodium dodecyl sulfate (SDS) and sodium stearate (SS) were selected for a Design of Experiments (DoE) approach, as shown in Fig. 3. This DoE investigated the influence of the solution flow rate and % (w/w) additive on the polymorphism of CBZ obtained by the SASD process, as reported in Table 4. The pressure used for both of these DoE approaches was 12.0 MPa. This was as a result of higher pressures (17.0 MPa) from the screening runs in Table 3 resulted in blockages of the nozzle due to significant precipitation taking place prior to passing...
through the small volume (0.01 cm$^3$) nozzle.

**Figure 3.** Design of Experiment (DoE) schematic to investigate the effect of additive quantity and solution flow rate on the polymorphic forms of CBZ obtained by the SASD process.
Table 4. Experimental Conditions Used in SASD Runs for a Design of Experiments (DoE) using Sodium Dodecyl Sulfate (SDS) and Sodium Stearate (SS) as Additives

<table>
<thead>
<tr>
<th>DoE Point</th>
<th>Sample Reference</th>
<th>Additive Used</th>
<th>%Additive (w/w)</th>
<th>Solution Flow Rate $F_{\text{Solution}}$ (ml/min)</th>
<th>Solution Flow Rate $F_{\text{Solution}}$ (g/min)</th>
<th>Flow Ratio Solution/SCF $R_{\text{Flow Ratio}}$</th>
<th>Solid Form Obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SASD 12</td>
<td>SDS</td>
<td>1</td>
<td>0.10</td>
<td>0.079</td>
<td>0.005</td>
<td>I and III</td>
</tr>
<tr>
<td>2</td>
<td>SASD 13</td>
<td>SDS</td>
<td>10</td>
<td>0.10</td>
<td>0.079</td>
<td>0.005</td>
<td>I and III</td>
</tr>
<tr>
<td>3</td>
<td>SASD 14</td>
<td>SDS</td>
<td>10</td>
<td>0.40</td>
<td>0.316</td>
<td>0.021</td>
<td>I and III</td>
</tr>
<tr>
<td>4</td>
<td>SASD 15</td>
<td>SDS</td>
<td>1</td>
<td>0.40</td>
<td>0.316</td>
<td>0.021</td>
<td>III</td>
</tr>
<tr>
<td>5</td>
<td>SASD 8</td>
<td>SDS</td>
<td>5</td>
<td>0.25</td>
<td>0.198</td>
<td>0.013</td>
<td>I and III</td>
</tr>
<tr>
<td>6</td>
<td>SASD 16</td>
<td>SS</td>
<td>1</td>
<td>0.10</td>
<td>0.079</td>
<td>0.005</td>
<td>I and II</td>
</tr>
<tr>
<td>7</td>
<td>SASD 17</td>
<td>SS</td>
<td>10</td>
<td>0.10</td>
<td>0.079</td>
<td>0.005</td>
<td>I and II</td>
</tr>
<tr>
<td>8</td>
<td>SASD 18</td>
<td>SS</td>
<td>10</td>
<td>0.40</td>
<td>0.316</td>
<td>0.021</td>
<td>I and II</td>
</tr>
<tr>
<td>9</td>
<td>SASD 19</td>
<td>SS</td>
<td>1</td>
<td>0.40</td>
<td>0.316</td>
<td>0.021</td>
<td>I and II</td>
</tr>
<tr>
<td>10</td>
<td>SASD 6</td>
<td>SS</td>
<td>5</td>
<td>0.25</td>
<td>0.198</td>
<td>0.013</td>
<td>II</td>
</tr>
</tbody>
</table>

*For all DoE runs, concentration of CBZ in methanol was 50 mg/ml, temperature was 50°C, pressure was maintained at 12.0 MPa and CO$_2$ flow rate was kept at approximately 15.0 g/min (30 ml/min). %Additive: proportion of additive used in each experimental run; $F_{\text{Solution}}$: solution flow rate; $R_{\text{Flow Ratio}}$: mass flow-rate ratio of the solution to SCF (CO$_2$).

Conventional spray drying

All samples (SD 1 to 6) were spray dried by a Büchi B-290 mini spray dryer. The inert loop
was enabled in conjunction with a condenser at −20 °C to facilitate the use of organic solvents.

The CBZ solid particles were collected by a high efficiency cyclone. A 2-fluid nozzle with 0.7 mm cap was employed for atomizing the methanol solutions containing CBZ with/without additives. Nitrogen was selected as the atomizing gas with flow rate of ∼473 NL/h (P = 0.10 mPa and T = 0°C) and the aspirator was set to 100 % (35.0 m3/h). The final spray dried powders were collected and transferred to a desiccator after production until further characterization. A list of all the experiments performed using the Büchi B-290 mini spray dryer are reported in Table 5.

Table 5. Experimental Conditions used in Conventional Spray Drying (SD) Runs and List of Carbamazepine (CBZ) Solid Forms Obtained

<table>
<thead>
<tr>
<th>Sample Reference</th>
<th>Additive Used</th>
<th>%Additive (w/w)</th>
<th>(C_{[CBZ]}) (mg/ml)</th>
<th>Solid Form Obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD 1</td>
<td>No additive</td>
<td>-</td>
<td>50.0</td>
<td>IV</td>
</tr>
<tr>
<td>SD 2</td>
<td>SS</td>
<td>5</td>
<td>50.0</td>
<td>IV</td>
</tr>
<tr>
<td>SD 3</td>
<td>SDS</td>
<td>5</td>
<td>50.0</td>
<td>IV</td>
</tr>
<tr>
<td>SD 4</td>
<td>No additive</td>
<td>-</td>
<td>17.0</td>
<td>IV</td>
</tr>
<tr>
<td>SD 5</td>
<td>SS</td>
<td>5</td>
<td>17.0</td>
<td>IV</td>
</tr>
<tr>
<td>SD 6</td>
<td>SDS</td>
<td>5</td>
<td>17.0</td>
<td>IV</td>
</tr>
</tbody>
</table>

\(d\) For all runs, outlet temperature was 50 °C. %\(\text{Additive}\): quantity of additive used; \(C_{[CBZ]}\): concentration of carbamazepine (CBZ) in methanol.

Solid-state characterization

Powder X-Ray Diffraction (PXRD) in reflection mode was performed using an Empyrean diffractometer (PANalytical, Phillips) with Cu K\(\alpha\) radiation (\(\lambda = 1.5406 \ \text{Å}\)) at room
temperature. Samples were lightly pressed on a zero-background disc and placed on a sample
holder. Each spectrum was recorded at a tube voltage of 40 kV and a tube current of 40 mA,
with a step size of 0.02 ° (2θ) and a scan speed of 0.102° (2θ·s⁻¹) in the angular range of 5° to
30° (2θ) with 4 rpm.

Scanning electron microscopy (SEM) analysis was performed on a Hitachi SU-70 system
operating at 10 kV. Samples were mounted onto aluminum stubs with double-sided carbon
tape. The stubs were placed inside a gold sputter coater (Emitech K550X) and coated with a
plasma current of 20 mA for two minutes.

Results and Discussion

Precipitation of carbamazepine in a batch supercritical antisolvent process

The precipitation of carbamazepine (CBZ) by supercritical antisolvent crystallization was
experimentally observed in a batch high-pressure vessel, prior to performing supercritical CO₂
antisolvent-assisted nano spray drying (SASD) experiments. These batch precipitation
experiments contributed to our understanding of the pressures and the solution to CO₂
antisolvent mass ratios necessary to induce supersaturation and consequently antisolvent
nucleation of CBZ in the mixing chamber of the SASD nozzle. A range of ±5 °C of the
operating temperature in the batch supercritical antisolvent process was selected to account for
any possible temperature drop (caused by heat loss in the nozzle due to the Joule-Thomson
effect) or increase (caused by an overcompensation of the heating resistors in the nozzle). Table
6 shows that at solution to CO₂ ratios between 0.49-0.55, precipitation of CBZ occurred due to
antisolvent crystallization inside the batch vessel using the selected temperature ranges.

Table 6. Experimental Conditions Required for the Precipitation of Carbamazepine in a
Batch Supercritical Antisolvent Process ε
<table>
<thead>
<tr>
<th>$t$ (°C)</th>
<th>$P$ (MPa)</th>
<th>$R_{\text{Mass Ratio}}$ Solution/SCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>8.72 ± 0.04</td>
<td>0.55</td>
</tr>
<tr>
<td>50</td>
<td>9.66 ± 0.01</td>
<td>0.50</td>
</tr>
<tr>
<td>55</td>
<td>10.17 ± 0.10</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*For all precipitation tests, concentration of CBZ in methanol was 50 mg/ml, stirring rate was 600 rpm and pressure was increased at a rate of 1 MPa/min until reaching the final pressure. $P$: pressure in the batch pressure vessel; $t$: temperature in the air chamber; $R_{\text{Mass Ratio}}$: mass ratio of solution to supercritical fluid (CO$_2$).*

**Production of CBZ nanoparticles by the supercritical CO$_2$ antisolvent-assisted nano spray drying (SASD) method with/without additives**

In order to ensure that the primary crystallization mechanism in the SASD method would be initiated by antisolvent supersaturation/nucleation in the nozzle, a working pressure of 17.0 MPa was selected for all screening experiments (mass flow ratio of solution to supercritical fluid is 0.013 which is suitable to induce supersaturation). Despite a short residence time of the fluids (CO$_2$ and drug solution) in the SASD nozzle, some blockages occurred at this high pressure. As a result, the pressure was reduced to 12.0 MPa (mass flow ratio of solution to supercritical fluid is between 0.005-0.021) which is still sufficient to induce supersaturation by the CO$_2$ antisolvent effect, and helps minimizing any blockages in the SASD nozzle due to crystal growth of CBZ.

The aim of this work is to investigate whether CBZ polymorphism can be controlled in a continuous supercritical crystallization process, as previously demonstrated in a batch supercritical crystallization process$^{26}$. Padrela *et al.* showed that form II and form III of CBZ could be obtained using a batch supercritical process when using the anionic additives, sodium stearate and sodium dodecyl sulfate, respectively. $^{26}$ Prior to investigating whether additives...
could control the polymorphic form of CBZ during the supercritical CO$_2$ antisolvent-assisted nano spray drying (SASD) process, three control experiments were completed at each of the different solutions rates used in this study without the use of additives. It must be noted that the nano/sub-micron size range of the CBZ particles, as described by the Scherrer equation, influences the broadness of the PXRD peaks observed throughout this study.
Figure 4. Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, and III) from the Cambridge Structural Database (CSD)\textsuperscript{64-66} and CBZ samples processed without additives in a SASD process at various solution flow rates.

Figure 4 shows that the metastable form I, with small impurities from the stable form III, of CBZ was produced at each flow rate without the use of additives. This result would serve as a control to investigate if certain additives have an effect on the polymorphism of CBZ using the SASD process.

A preliminary SASD screening with the additives reported in Table 3 appeared to uphold the reported results by Padrela \textit{et al.} for certain additives in their batch supercritical process.\textsuperscript{26} Each experiment presented in Table 3 and Fig. 5 was repeated at least three times.
Figure 5. Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, and III) from the Cambridge Structural Database (CSD)\textsuperscript{64-66} and CBZ samples processed with additives produced by the SASD method (SASD 4-11), reported in Table 3.

The results obtained from the screening runs presented in Fig. 5 show that (1) amorphous CBZ was obtained when using Ethyl Cellulose (SASD 7) as additives, (2) PXRD-pure CBZ form I was obtained when using either Maltitol (run SASD 5) or L-Eudragit 100-55 (run SASD 9) as additives, (3) PXRD-pure CBZ form II was obtained when using sodium stearate (run SASD 6) as additive, and (4) PXRD-pure CBZ form III was obtained when using sodium dodecyl sulfate (run SASD 8) as an additive. The anionic additives sodium stearate (which promotes
the form of CBZ form II) and sodium dodecyl sulfate (which promotes the formation of CBZ form III) were selected for further investigation. A Design of Experiments (DoE) approach was applied for each additive to determine if the results obtained would be as robust across a range of distinct processing conditions. The processing parameters selected for this DoE study were; i) the % of additive (w/w) used and ii) the solution flow rate. Additive quantity was selected as a parameter to investigate if a minimum and maximum threshold could be determined where the additive would have an effect on the final polymorphic form obtained. Solution flow rate was selected as a parameter due to its ability to vary the solution to supercritical CO$_2$ antisolvent mass flow ratio, as observed in Table 2. This ratio is expected to affect the supersaturation of the CBZ solution in the SASD nozzle, which may influence the polymorph obtained. This ratio may also provide an insight into the crystallization mechanism involved in our SASD experiments which will be discussed in this manuscript.

The primary crystallization mechanism is predicted to be antisolvent nucleation/crystallization, induced by high supersaturation levels inside the high-pressure SASD nozzle. This prediction stems from the results obtained in the precipitation of carbamazepine in a batch supercritical antisolvent process. As the pressure increases, the solvating power and the miscibility of CO$_2$ with methanol increase, causing CBZ to precipitate. An alternative mechanism for the production of these CBZ nanoparticles is the evaporation of solvent during the spray drying step in the drying chamber. This drying step is necessary in this process to remove the solvent (methanol) from the atomized suspension droplets and convert them into a fine dried powder. The removal of solvent must be efficient to prevent any polymorphic conversion of CBZ in the final samples. In attempts to replicate the antisolvent mechanism observed in the batch precipitation process, a solution to CO$_2$ mass flow ratio of 0.011 was used, which falls below the maximum allowed ratio of 0.5 for antisolvent crystallization to occur at a working temperature of 50 ºC (see Table 6). At the end of these experiments, upon disassembling the
apparatus, a small portion of fine powder was observed inside the mixing chamber of the SASD nozzle, indicating that antisolvent nucleation/crystallization of CBZ occurred in the screening experiments.

Figure 6 presents a Design of Experiments (DoE) to investigate the effect of additive (sodium dodecyl sulfate) quantity and solution flow rate on the polymorphic forms of CBZ obtained by SASD.

Figure 6. a) Design of Experiments (DoE) schematic to investigate the effect of additive (sodium dodecyl sulfate) quantity and solution flow rate on the polymorphic forms of CBZ obtained by supercritical antisolvent assisted nano spray drying (SASD). b) Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, III and IV) from the Cambridge Structural Database (CSD) and CBZ samples processed through SASD with SDS as the additive. Asterisks (*) represent unidentified peaks (9° 2 Theta) that cannot be
attributed to any CBZ polymorph or additive. Experimental conditions as described in Table 4.

Figure 6 shows that the process parameters studied in this DoE (e.g. solution flow rate, % of additive) do not seem to significantly influence the polymorphic outcome of carbamazepine. In a batch supercritical antisolvent process, SDS favors the formation of pure form III of CBZ. Similarly, in a continuous antisolvent-assisted nano spray drying process, form III of CBZ is consistently obtained for the different ratios of additive (SDS) and solution flow rates used (Fig. 6). However, Fig. 6 shows the presence of small amounts of impurity peaks at ca. 12° (2 Theta) corresponding to CBZ form I at DoE Points 1, 2, 3 and 5. This impurity corresponds to the dominant form obtained when additives were not used. Interestingly, an unknown peak at ca. 9° (2 Theta) appears in the powder X-ray diffractograms of the samples produced in the DoE points 1 to 5 (Fig. 6). This peak requires further investigation to explore the reason for its appearance when using SDS. This result (obtaining the stable form III) is of particular interest as the time between nucleation and precipitation in the SASD nozzle is in the range of milliseconds, and as a result, it is typically difficult to obtain a stable polymorph. This is due to the fact that according to Ostwald’s rule, it is not the most stable but the least stable polymorph that crystallizes first. Indeed, supercritical CO₂ methods typically favor the formation of metastable crystalline forms most likely due to the peculiar/unique antisolvent effect of CO₂. Comparatively, conventional spray drying is a flash process (without using CO₂) that is typically used to produce amorphous samples, which represent the least thermodynamically stable forms of an API.

Table 4 also shows the experimental conditions used for this DoE using SS, including the ratio of solution to SCF which will be discussed in further detail later in this section. Figure 7 presents a schematic of the DoE studied when SS was used as the additive in the SASD experiments.
Figure 7. a) Design of Experiments (DoE) schematic to investigate the effect of additive (sodium stearate) quantity and solution flow rate on the polymorphic forms of CBZ obtained by supercritical antisolvent assisted nano spray drying (SASD). b) Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, III and IV) from the Cambridge Structural Database (CSD)\textsuperscript{64-67} and CBZ samples processed through SASD with sodium stearate as the additive. Experimental conditions as described in Table 4.

Figure 7 shows that the % of SS influences the polymorphism of CBZ nanoparticles produced by supercritical antisolvent assisted nano spray drying (SASD). All samples processed with SS resulted in the generation of CBZ form II as the dominant polymorph observed. At low quantities (1%), the presence of small peaks corresponding to CBZ form I are observed while at higher quantities (10%), the form I impurities begin to decrease but are not completely removed. At the mid-point (DoE Point 10), pure form II was observed which may represent
the optimum quantity of additive required to control the polymorphic form of CBZ. The results from Fig. 7 indicate that the results previously obtained by Padrela et al., demonstrating that SS results in the templating of CBZ molecules to generate form II, is upheld when selecting the SASD technique. Although most samples generated are not PXRD pure, the presence of minor impurities (of CBZ form I) from other polymorphic forms are likely the cause of the technique used. When additives are not used, there is a tendency to generate CBZ form I (seen in Fig. 4) and this may be the cause of these minor impurities observed in Fig. 7. Both parameters (quantity of additive and solution flow rate) do not appear to influence the polymorphic form generated in all samples when selecting this additive.

**SASD versus conventional spray drying**

An important aspect that distinguishes the SASD process from conventional spray drying (which typically uses N$_2$ to dry a solution) concerns the unique precipitation mechanism induced by the antisolvent effect of supercritical CO$_2$ in the coaxial nozzle. The supersaturation/antisolvent mechanism induced by supercritical CO$_2$ provides a unique feature to spray drying processes to control drug polymorphism. In a Buchi conventional spray dryer, there is no antisolvent crystallization occurring in the nozzle, with solvent evaporation being the governing precipitation mechanism happening during the spray drying step. The low miscibility of the N$_2$ as well as the poor anti-solvent power provides a good assessment of the anti-solvent performance of CO$_2$. Therefore, any differences between the polymorphic forms of CBZ obtained from conventional spray drying and the SASD process would strongly suggest that the mechanism that governs crystallization and polymorphic control in SASD is caused by the antisolvent effect of CO$_2$.

Table 5 shows the experimental conditions used in the conventional spray drying (SD) where the additives sodium stearate and sodium dodecyl sulfate were used. Figure 8 presents powder
X-ray diffraction patterns for CBZ samples (with/without additives) processed by SASD and conventional spray drying methods.

Figure 8. Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, III and IV) from the Cambridge Structural Database (CSD)\textsuperscript{64-67} and CBZ samples (with/without additives) processed by supercritical antisolvent assisted nano spray drying (SASD) and conventional spray drying (SD) methods. When additives were selected, the quantity was 5% w/w (2.5 mg/ml).
Using processing conditions in conventional spray drying (SD) as similar as possible to the supercritical antisolvent assisted nano spray drying (SASD) processing conditions (outlet temperature of 50°C; 50 mg/ml of CBZ in methanol), it was observed that the metastable form IV of CBZ was obtained by SD which differed from the polymorph produced using the SASD technique (CBZ form I). The result obtained from conventional spray drying corresponds well with the results obtained by Halliwell et al. that concluded that this technique is a robust method for the production of form IV of CBZ. Interestingly, when either sodium stearate (SS) or sodium dodecyl sulfate (SDS) were used in the conventional spray drying (SD) experiments, form IV was also obtained. However, form II (when using SS as the additive) and form III (when using SDS as the additive) were the primary forms obtained in SASD. These results suggest that anionic molecular additives influence the polymorphism of CBZ specifically when supersaturation is generated by the CO₂ antisolvent effect.

The SEM analysis in Fig. 9 confirms the expected shape for each crystal form produced. Carbamazepine nanoparticles processed with SS by the SASD method display a long needle-shape (Fig. 9c) which is characteristic of form II. Block-shaped particles (Fig. 9d) were observed for CBZ samples processed with SDS, which corresponded to the form III. Needle-shape particles (Fig. 9b) in the form of aggregates belonging to form I were produced without the use of additives.
Figure 9. Scanning electron microscopy (SEM) images of raw CBZ and CBZ samples produced from different SASD runs: a) raw CBZ as form III; b) CBZ form I produced without additives (SASD 4); c) CBZ form II produced with sodium stearate (SASD 6); d) CBZ form III produced with sodium dodecyl sulfate (SASD 8).

Particle size analysis varied depending on the polymorphic form obtained. Due to the needle-like shape of CBZ forms I and II, the width was determined which resulted in a much lower mean particle size than form III particles (block-shaped). SASD processed Form I samples showed a mean particle size of 120 ± 37 nm while form II particles showed an average size of 94±39nm. Form III particles showed a mean size of 1 ± 0.42 µm, primarily due to the difference in shape. The Gaussian distribution of each sample is provided in the Supporting Information (Figs. SI1, SI2, SI3 and SI4). The particle size of the raw CBZ samples (form III) was also
analyzed, which was determined to be 59±13µm. This highlights the potential of the SASD method for the production of nano-sized particles of pharmaceutical drugs.

A final confirmation that antisolvent supersaturation/nucleation is likely to occur in the nozzle during the SASD experiments relates to the mass flow-rate ratio of solution and supercritical CO$_2$ when compared to the mass ratio obtained in a batch supercritical antisolvent process. For the precipitation tests presented in Table 6, the mechanism that caused precipitation of CBZ was CO$_2$ antisolvent crystallization. The ratio of solution to supercritical CO$_2$ should allow us to determine the minimum value needed for antisolvent crystallization to occur. Calculating the mass ratios of solution to supercritical CO$_2$ in the batch supercritical process was completed, as described in the Experimental Section. In the batch supercritical antisolvent process, there was a mass ratio of solution to supercritical CO$_2$ of 0.49-0.55 (depending on the temperature used) required to achieve for the precipitation of CBZ from methanol solutions.

At the median solution flow rate (0.25 ml/min) and at 50 °C, the flow-rate ratio of solution to supercritical CO$_2$ used was 0.013 (SASD 2 in Table 2), which shows that there is a significantly higher proportion of CO$_2$ than solution inside the nozzle. As this value is significantly less than 0.50 (the maximum mass ratio allowed for antisolvent crystallization of CBZ to occur in a batch reactor at 50 °C), there is a strong indication that supersaturation of the CBZ solutions occurs in the SASD nozzle, caused by the CO$_2$ antisolvent effect. This supersaturation of the CBZ solutions induced by the CO$_2$ antisolvent effect, associated with the presence of each additive, promotes the nucleation of a particular polymorph of CBZ in the nozzle, followed by its crystallization in the drying chamber.

In order to test this hypothesis, the concentration of CBZ in methanol was reduced to 1/3 of the initial value (17.0 mg/ml) and processed using the SASD technique (see Table 3). Figure 10 shows the PXRD diffractograms of CBZ samples produced from low concentration CBZ methanol solutions ($C_{[CBZ]} = 17.0$ mg/ml) by the SD and SASD methods.
Figure 10. Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, III and IV) from the Cambridge Structural Database (CSD)\(^{64-67}\) and CBZ samples processed using SASD and conventional spray drying (SD) methods. A low concentration of CBZ in the methanol solutions was used (17.0 mg/ml), as described in Tables 3 and 5. When additives were selected, the quantity used was 5% w/w (0.8 mg/ml).

The SASD experiments yielded amorphous CBZ samples, regardless of whether an additive was used. This shows that as we decrease the concentration of CBZ in the methanol solutions,
the levels of supersaturation achieved inside the SASD nozzle are significantly reduced which
does not promote nucleation and crystallization of CBZ. By reducing the concentration of the
CBZ solutions (to 17.0 mg/ml of CBZ in methanol), supersaturation of CBZ in the SASD
nozzle is unlikely to occur, which leads to the amorphization of CBZ during the spray drying
step (after the nozzle exit). Using identical concentrations of CBZ in methanol and similar
operating conditions in a conventional spray dryer resulted in CBZ form IV. As there is no
antisolvent supersaturation occurring in the conventional spray drying (SD) process (rather
solvent evaporation being the main precipitation mechanism in this method), this result further
supports our hypothesis that antisolvent supersaturation is the governing precipitation
mechanism in the supercritical CO$_2$ antisolvent-assisted nano spray drying (SASD) method.
The stability of CBZ samples produced by the SASD process is presented and discussed in
detail in the Supplementary Information.

Conclusions
This work demonstrates that the polymorphic outcome of carbamazepine (CBZ) is controllable,
with only minor polymorphic impurities, using anionic additives in a continuous supercritical
CO$_2$ assisted nano spray drying process (SASD). Both SEM and PXRD results show that using
sodium stearate promotes the formation of CBZ form II across a range of processing conditions
(e.g. solution flow-rate and % of additive used) in the SASD process, while sodium dodecyl
sulfate promotes the formation of the stable CBZ form III. The results presented herein suggest
that the primary mechanism that governs the crystallization of CBZ in the SASD process is the
occurrence of supersaturation in the nozzle caused by the antisolvent effect of supercritical
CO$_2$. We suggest that the anionic additives used in this work template form II (when using
sodium stearate as an additive) or form III (when using sodium dodecyl sulfate as an additive)
of CBZ during the nucleation stage in the SASD nozzle. This leads to the crystallization of
each particular polymorph during the spray-drying step (after the nozzle exit). Additionally, the ratio of solution to supercritical CO\(_2\) is considerably high in the SASD process when compared to the values obtained in the batch supercritical antisolvent experiments, strongly indicating that antisolvent nucleation should be occurring in the nozzle. These results could not be replicated when using similar processing conditions in conventional spray drying (where antisolvent supersaturation does not occur). The difference in mechanisms between these the SASD and the SD methods is clearly observed by the different polymorphic outcomes of CBZ obtained. Depending on the additive used, the SASD process produces forms I, II or III, while conventional spray drying consistently produces form IV only, irrespective of the additive selected. In addition to this, when the concentration of the CBZ solution is reduced, supersaturation in the SASD nozzle is unlikely to be achieved and, as a result, antisolvent nucleation/crystallization would not occur in the SASD process (amorphous CBZ samples are produced) while the metastable form IV of CBZ is consistently produced when using conventional spray drying (SD).

**Acknowledgements**

This work was undertaken as part of the Synthesis and Solid State Pharmaceutical Centre supported by the Science Foundation Ireland (SFI) and is co-funded under the European Regional Development Fund (Grants SFI SSPC2 12/RC/2275 and 15/US-C2C/I3133).

**Supporting Information**

Supporting information is available for this manuscript. Image analysis (SEM), particle size distributions and solid-state stability (analyzed by PXRD) are provided for selected CBZ samples (forms I, II and III) produced by continuous supercritical CO\(_2\) assisted nano spray drying (SASD).
References


List of Figures

Figure 1. Schematic diagram of the batch supercritical antisolvent apparatus used for solubility testing. 1, CO$_2$ cylinder; 2, gas compressor; 3, temperature controlled air chamber; 4, stainless steel storage cylinder; 5, magnetic stirrer plate; 6, high-pressure vessel; 7, exit valve; Pc: pressure controller; Tc: temperature controller.

Figure 2. Schematic diagram of the continuous SASD apparatus. 1, CO$_2$ cylinder; 2, gas compressor; 3, CBZ solution flask connected to a HPLC pump; 4, temperature-controlled CO$_2$ storage cylinder; 5, high-pressure nozzle; 6, drying chamber; 7, filter; 8, Temperature controlled air chamber; Tc: temperature controller; Pc: pressure controller.

Figure 3. Design of Experiment (DoE) schematic to investigate the effect of additive quantity and solution flow rate on the polymorphic forms of CBZ obtained by the SASD process.

Figure 4. Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, and III) from the Cambridge Structural Database (CSD) and CBZ samples processed without additives in a SASD process at various solution flow rates.

Figure 5. Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, and III) from the Cambridge Structural Database (CSD) and CBZ samples processed with additives produced by the SASD method (SASD 4-11), reported in Table 3.

Figure 6. a) Design of Experiments (DoE) schematic to investigate the effect of additive (sodium dodecyl sulfate) quantity and solution flow rate on the polymorphic forms of CBZ obtained by supercritical antisolvent assisted nano spray drying (SASD). b) Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, III and IV) from the Cambridge Structural Database (CSD) and CBZ samples processed through SASD with SDS as the additive. Asterisks (*) represent unidentified peaks (9° 2 Theta) that cannot be attributed to any CBZ polymorph or additive. Experimental conditions as described in Table 4.
**Figure 7.** a) Design of Experiments (DoE) schematic to investigate the effect of additive (sodium stearate) quantity and solution flow rate on the polymorphic forms of CBZ obtained by supercritical antisolvent assisted nano spray drying (SASD). b) Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, III and IV) from the Cambridge Structural Database (CSD)\textsuperscript{64-67} and CBZ samples processed through SASD with sodium stearate as the additive. Experimental conditions as described in Table 4.

**Figure 8.** Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, III and IV) from the Cambridge Structural Database (CSD)\textsuperscript{64-67} and CBZ samples (with/without additives) processed by supercritical antisolvent assisted nano spray drying (SASD) and conventional spray drying (SD) methods. SS – sodium stearate; SDS – sodium dodecyl sulfate.

**Figure 9.** Scanning electron microscopy (SEM) images of raw CBZ and CBZ samples produced from different SASD runs: a) raw CBZ as form III; b) CBZ form I produced without additives (SASD4); c) CBZ form II produced with sodium stearate (SASD 6); d) CBZ form III produced with sodium dodecyl sulfate (SASD 8).

**Figure 10.** Powder X-ray diffraction patterns of theoretical CBZ polymorphic forms (I, II, III and IV) from the Cambridge Structural Database (CSD)\textsuperscript{64-67} and CBZ samples processed using SASD and conventional spray drying (SD) methods. A low concentration of CBZ in the methanol solutions was used (17.0 mg/ml), as described in Tables 3 and 5. SS: sodium stearate; SDS: sodium dodecyl sulfate.
List of Tables

Table 1. Type of Additives Used in the Preparation of Carbamazepine Solutions in Methanol for Supercritical-CO$_2$ Antisolvent-Assisted Nano Spray Drying

Table 2. List of Carbamazepine (CBZ) Solid Forms Obtained at Different Solution Flow Rates Without the Use of Additives Using Supercritical CO$_2$ Antisolvent-Assisted Nano Spray Drying (SASD) $^a$

Table 3. List of Carbamazepine (CBZ) Solid Forms Obtained Using Supercritical CO$_2$ Antisolvent-Assisted Nano Spray Drying (SASD) $^b$

Table 4. Experimental Conditions Used in SASD Runs for a Design of Experiments (DoE) using Sodium Dodecyl Sulfate (SDS) and Sodium Stearate (SS) as Additives $^c$

Table 5. Experimental Conditions used in Conventional Spray Drying (SD) Runs and List of Carbamazepine (CBZ) Solid Forms Obtained$^d$

Table 6. Experimental Conditions Required for the Precipitation of Carbamazepine in a Batch Supercritical Antisolvent Process $^e$
Controlling Polymorphism of Carbamazepine Nanoparticles in a Continuous Supercritical CO₂-Assisted Spray Drying Process

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TOC Graphic
Synopsis

This work demonstrates a novel methodology to control the polymorphism of carbamazepine nanoparticles using a novel continuous supercritical CO$_2$ assisted nano spray drying (SASD) process. The type of additive used influenced the final polymorphic form of carbamazepine produced by SASD (when antisolvent supersaturation occurs in the nozzle) but not by conventional spray drying.