Preparation of Pharmaceutical Cocrystals Using Supercritical Carbon Dioxide

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1. Introduction (Times New Roman 11-point boldface)

It is estimated that about 33% of active pharmaceutical ingredients (APIs) in development are considered as Biopharmaceutics Classification System (BCS) Class 2 (low solubility, high permeability).[1–3] Kinetic solubility of BCS class 2 APIs can be improved through co-crystal formation and particle size reduction, among other approaches. Methods of co-crystal preparation with scale-up potential include batch crystallization, spray drying, and supercritical CO_2 ($scCO_2$) crystallization. There are a number of potential benefits to crystallization of an API or co-crystal by supercritical fluid (SCF) techniques. These can include a greener solvent choice, elimination of an additional drying step, removal of residual organic solvent, ability to adapt to a continuous process, and to produce small particle size with narrow particle size distribution without milling. For example, the rapid expansion from supercritical solution (RESS) process can be used to isolate particles much less than 1 µm diameter in a one-step crystallization process; i.e. no secondary milling step is required.[4]

In this work we present cocrystal formation of two anthelmintic compounds, praziquantel (PZQ) and niclosamide (NCS), using $scCO_2$. In one regard, the cocrystal formation occurs "spontaneously" (without mixing) in supercritical conditions, despite very low solubility of both API (NCS) and coformer (urea). While in the other regard, the API (PZQ) and coformer(s) are soluble in $scCO_2$ and cocystals with small particle size are prepared by RESS. The impact of processing conditions on cocrystal phase purity and particle size is investigated.

2. Materials and Methods

Praziquantel (>98% purity, TCI America) and niclosmide (>98% purity, Millipore Sigma) were used without further purification. Coformers (urea, malonic acid, maleic acid, glutaric acid, malic acid, succinic acid, 4-hydroxybenzoic acid (4-HBA), L-alanine, nicotinamide, and vanillin, all > 98% purity) were sourced from Millipore Sigma. Liquid CO_2 (99.9% with eductor) was sourced from Praxair, Inc. Solvents were sourced form Fisher Chemical and Sigma Aldrich.

All experiments were conducted in a modified SFT-110 equipment. For each experiment, the vessel was pressurized with CO_2 using an SFT-10 pump and the vessel was sealed by closing the valves at the inlet and outlet. The pressure in the vessel was measured at 5 min increments using an in-line monitoring system comprising a PX309-10KGI pressure transducer (Omega) and an OM-CP-Process101A current data logger (Omega). The vessel was held at the specified temperature and pressure for a designated time. Depending on the experiment, the solubilized solids were collected in the collection vials through a RESS process or residual solids remaining in the vessel were collected and analyzed. Analysis techniques included X-ray powder diffraction (XRPD), microscopy, differential scanning calorimetry (DSC).

3. Results and discussion

PZQ exhibited moderate solubility in $scCO_2$ ($0.48 - \geq 4.2\times10^{-4}$ mol. fraction) and easily formed cocrystals using conventional methods. PZQ can be solubilized in $scCO_2$ and the solubility was improved at similar pressure by about an order of magnitude through addition of approximately 10% co-solvent. On the other hand, NCS exhibited poor solubility in $scCO_2$ and $scCO_2$ with 10% cosolvent. A summary of select solubility results are shown in Table 1.

Table 1- Approximate solubility of PZQ and NCS in $scCO_2$ and CO_2 with ~10% cosolvent at 40 °C.

API	Pressure, MPa	Co-solvent	Solubility, mol fraction Y × 10^4
PZQ	12.9	-	0.48
	18.1	-	3.41
	33.6	-	> 4.21
	10.2	acetone	3.75
	11.9	DCM	4.54
	12.4	THF	1.96
NCS	20	-	0.02
	15	acetone	0.48
	15	THF	0.41

Despite its low solubility, NCS was found to form a cocrystal with urea in supercritical conditions without mixing. Using XRPD and chemometric analysis, it was found that in subcritical CO_2 the cocrystal did not form but in $scCO_2$ the amount of conversion was approximately equal, independent of pressure. Hydrogen bonding calculations and molecular dynamics simulations are in progress to understand the spontaneous conversion in the presence of $scCO_2$. Control experiments in dry, humid, and elevated temperature conditions indicate that the presence of $scCO_2$ is a key contributor to the spontaneous cocrystal formation because cocrystal was not observed in control experiments.

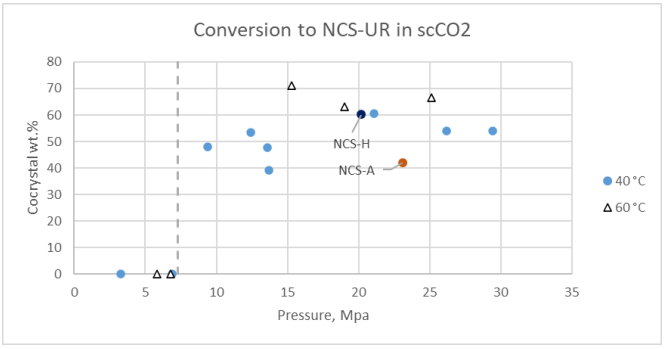

Figure 1- Conversion to NCS-urea cocrystal based on XRPD. Critical pressure (7.3 MPa) indicated on the plot with a dashed line.

A brief cocrystal screening using conventional solvents (acetone and EtOH) found that PZQ readily formed cocrystals with malonic acid, glutaric acid malic acid, succinic acid, 4-HBA, and vanillin. Work is underway to identify appropriate conditions to prepare a phase-pure PZQ cocrystal with small, uniform particles by RESS or RESS with cosolvent. The solubility of PZQ and coformer will be used to guide the design and understand results of crystallization experiments.

4. Conclusions

As interest in using $scCO_2$ processing for pharmaceuticals grows, it is important to include similar processing conditions during the cocrystal screening process. In cases where API and coformer exhibit poor solubility in $scCO_2$, if the H-bonding affinity of the pair is strong, then a cocrystal may still spontaneously form using this solvent-free technique. Using the RESS method for cocrystal formation it is important to determine appropriate crystallization parameters based on the solubility of both components. Phase pure cocrystals may be obtained with small particle size, which can improve dissolution of BCS Class 3 compounds.

References

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