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FEELING THE PRESSURE: NANOPARTICLE CRYSTALLIZATION USING CONTROLLED EXPANSION OF SUPERCRITICAL SOLUTIONS

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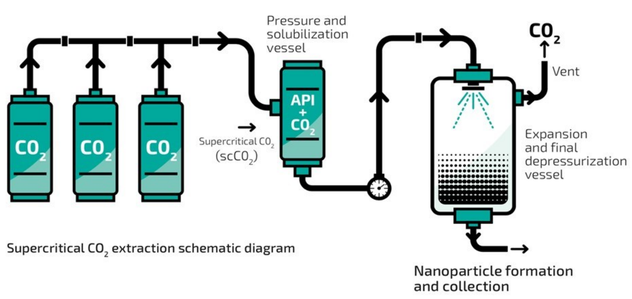
AIM

In this study, we have explored the crystallization of piroxicam (PRX) and budesonide (BUD) under pressure using supercritical carbon dioxide.

BACKGROUND

- Poor bioavailability and low efficacy arising from poor solubility are amongst the most common reasons for drug failure.
- Amorphous material typically has higher solubility than crystalline, but lower stability, which has led to the development of amorphous solid dispersions.
- Amorphous solid dispersions can offer increased dissolution rate but can still suffer from stability issues and the addition of polymer reduces drug loading within formulations.
- **Nanoforming** is based on Controlled Expansion of Supercritical Solution (CESS®) technology is a particle production method which is based on supercritical carbon dioxide ($scCO_2$).
- Nanoforming increases the specific surface area leading to higher dissolution rate whilst maintaining the stability of the crystalline form and avoiding the necessity for additional excipients.

CONTROLLED EXPANSION OF SUPERCRITICAL SOLUTION (CESS®)



- The bulk API was loaded into a pressure vessel and dissolved in $scCO_2$.
- From the pressure vessel the molecular mixture of CO_2 and API was guided to a nozzle.
- During expansion at the nozzle, the pressure and temperature of the supercritical CO_2 decreases leading into nucleation and growth of nanocrystals.
- Expansion leads also to the formation of CO_2 snow (i.e. dry ice) encapsulating formed nanocrystals protecting them and limiting agglomeration upon crystallisation.
- CO_2 is sublimated leaving only nanoformed dry API particles in the collection vessel.

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- Nanoform's cutting-edge sparse-data AI platform — STARMAP 2.0® — predicts the molecules most amenable to CESS®-powered nanoforming.
- Using structural information and thermal data, STARMAP can predict a molecule's solubility in $scCO_2$ and propensity to crystallize.
- Based on this, we can rank compounds in a given list to pick the winners as well as tune the manufacturing process.
- Using this approach BUD was identified as an ideal candidate.

BUDESONIDE

BUD is a medication of the corticosteroid type used to treat multiple indications with a variety of dosage forms including inhaled, oral pill, nasal spray and rectal forms.

BUD is a BCS class II drug with low water solubility (0.045 mg/mL) and low oral bioavailability (6-8%) due to high first pass effect.

BUD was run through the standard CESS process and nanoparticles with a D_{50} of ca. 50 nm were generated. However, XRPD analysis of the particles showed them to be amorphous.

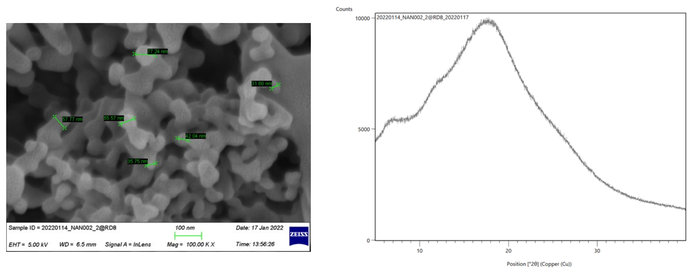

Figure 1 Particle size analysis by SEM and XRPD pattern of BUD post initial CESS processing.

The CESS process offers a number of opportunities to control crystallization and polymorphism:

- Temperature of Nanoforming.
- Presence of co-solvent.
- Choice of co-solvent.

Modification of the standard CESS process was undertaken using such crystallization aids, which was successful at generating crystalline material matching that of the supplied material, although with a larger particle size distribution that the amorphous.

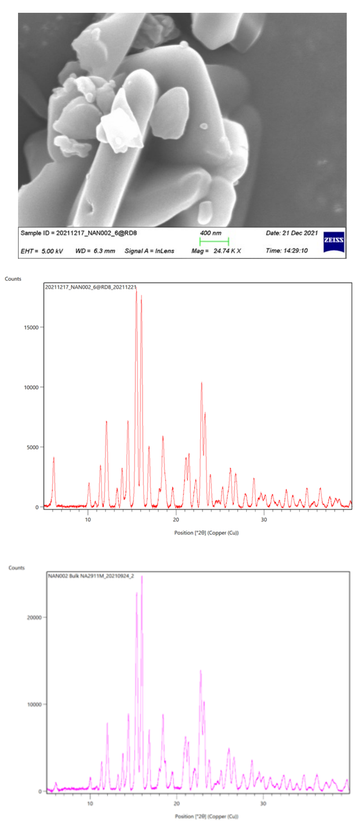

Figure 2 Particle size analysis by SEM (top) and XRPD pattern (middle) of BUD post initial CESS processing and XRPD pattern of supplied BUD (bottom).

CONCLUSIONS

Modification of the CESS process by was successful at generating crystalline budesonide, with highly crystalline material matching the known form generated.

PIROXICAM

PRX is a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class used to relieve the symptoms of painful inflammatory conditions like arthritis.

PRX has been shown to exhibit four anhydrous polymorphic forms, with Forms I and II being enantiotropic, and a monohydrate along with the amorphous.

Forms III and IV were identified by varying the cooling rate of molten PRX but crystallization processes for the generation of these metastable forms have not been reported.

Herein, we report a consistent crystallization protocol to generate metastable Form III using our CESS process. Running piroxicam through CESS using Temp 80 °C and Pressure 400 bar led to the crystallization of Form III with a consistent PSD D_{50} of sub 300 nm.

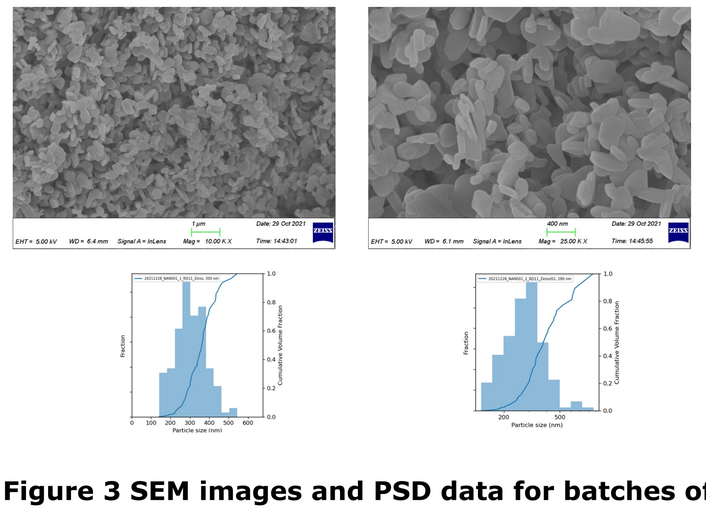

Figure 3 SEM images and PSD data for batches of nanoformed piroxicam.

This crystallization process has been successfully transferred to GMP conditions to generate multi-kilo quantities of nanoPRX.

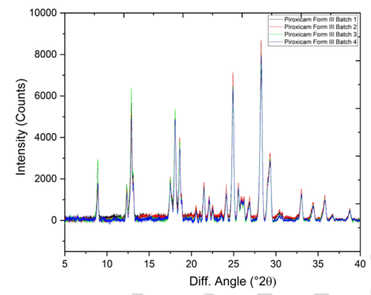

Figure 4 XRPD patterns of different GMP batches.

Dissolution studies of fast-dissolving oral tablets containing nanoPRX more rapid dissolution compared to micron sized particles. Furthermore, Phase 1 clinical trial data showed:

- Faster absorption of nanoformed formulation against the Felden® product containing micronized PRX.
- Equal absorption of nanoformed formulation against the Brexidol® product containing a β-cyclodextrin coupled PRX formulation.
- Lower standard deviation of absorption than that of both marketed products, which may mean less variability in the therapeutic response in patients.

CONCLUSIONS

A novel crystallization process using our CESS technology was developed to generate nanoparticles of metastable PRX Form III. These nanoparticles showed faster absorption in Phase 1 clinical trials over micron sized particles.

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