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Feeling the Pressure: Polymorphism, Particle Size and Morphology Control Through Nanoparticle Crystallization Using Controlled Expansion of Supercritical Solutions

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PURPOSE

Poor bioavailability and low efficacy arising from poor solubility are amongst the most common reasons for drug failure. Converting crystalline material to the amorphous form is an alternative means of improving solubility but physical stability of amorphous forms is a drawback in its applicability. An advanced approach is to use crystalline nanoparticles to improve drug solubility and increase the dissolution rate of active pharmaceutical ingredients (APIs).

The generation of crystalline nanoparticles can increase the specific surface area of API particles leading to higher dissolution rate whilst maintaining the stability of the crystalline form and avoiding the necessity for additional excipients, as is the case for an amorphous solid dispersion. Controlling crystalline form, morphology and particle size distribution (PSD) is critical for any crystallization process, even more so for nanoparticles.

METHODS

The key methodology for this work is Controlled Expansion of Supercritical Solution (CESS®) technology [1], which is a particle production method based on supercritical carbon dioxide ($scCO_2$) without the addition of further solvents. Atovaquone (ATO) and Fenofibrate (FEN) were the chosen APIs for the study owing to the presence of multiple polymorphic forms and their predicted high solubility in $scCO_2$.

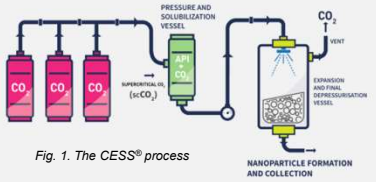

Fig. 1. The CESS® process

RESULTS

CESS® process

The CESS® technology allows particles size reduction down to hundred nanometer scale. An example is shown in Figure 2 where nanoparticles are compared with the starting material for ezetimibe.

Fenofibrate: particle sizing

In the case of FEN, the PSD of Form I can be controlled merely by varying the temperature at which crystallization occurs. In this way, the PSD can be tailored to the requirement of the desired dosage form without the need for separate processes or solvent systems being developed.

Atovaquone polymorphism

Through careful control of the CESS process, it is possible to manipulate the polymorphic form of ATO generated from the crystallization process using $scCO_2$, between Forms I, II and III, without the need for additional solvents.

Atovaquone morphology

Figure 5 demonstrates that the morphology of the nanoparticles of thermodynamically stable Form III can be modified from the lath preference of the larger particles to the more processable cubic shape.

Particle size reduction

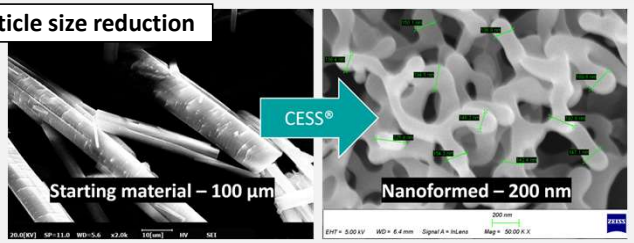

Fig. 2. Bulk material compared to nanoformed material.

Size control

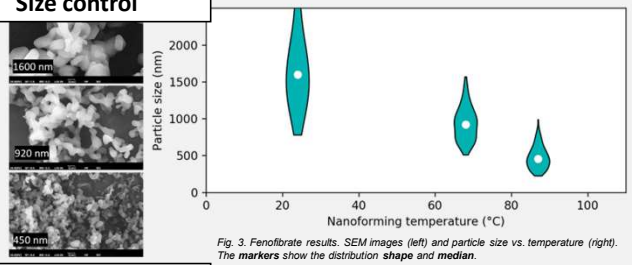

*Fig. 3. Fenofibrate results. SEM images (left) and particle size vs. temperature (right). The **markers** show the distribution **shape** and **median**.*

Polymorph control

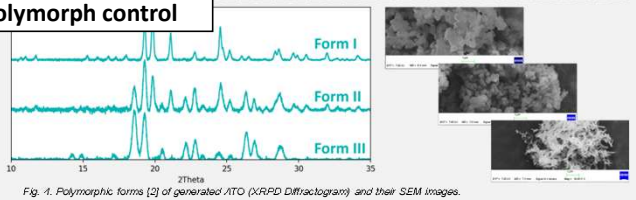

Fig. 4. Polymorphic forms [2] of generated ATO (XRPD Diffractogram) and their SEM images.

Morphology control

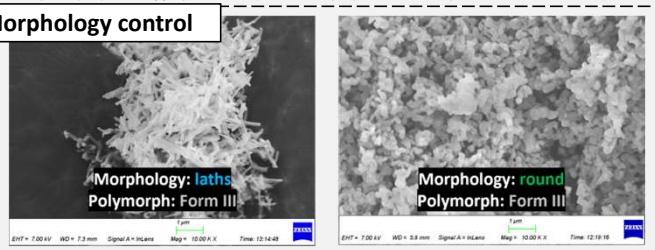

Fig. 5. Morphology control, generating either rods or spherical particles of the same polymorphic form.

CONCLUSIONS

By controlling the temperature of crystallization, it is possible to vary the PSD of crystalline FEN Form I from 0.5 to 1.5 µm in order to tailor the particles for a particular dosage form.

Through manipulation of the CESS process, it is possible to not only generate nanoparticles of metastable ATO Forms I and II but also to produce nanoparticles of the thermodynamically stable Form III with a modified, and more processable, morphology.

The versatility of CESS is truly remarkable, using the same process and the same solvent system it is possible to control the particle size, polymorphism and morphology merely by varying the process parameters.

Property	Benefit for Drug Development
Nanoparticles	Higher dissolution rate Higher bioavailability
Size control	Tuning for formulation
Polymorph control	Higher solubility Higher stability Intellectual property
Morphology control	Easier formulation

▲ *Table 1. Effect of the physical properties of the powder.*

References

[1] Pessi, J., Lassila, I., Meriläinen, A., Räikkönen, H., Hæggström, E., & Yliruusi, J. (2016). Controlled expansion of supercritical solution: a robust method to produce pure drug nanoparticles with narrow size-distribution. *Journal of pharmaceutical sciences*, *105*(8), 2293-2297.

[2] Tarur, Venkataswubramanian. "Novel polymorphs of atovaquone and process of." U.S. Patent Application No. 10/569,036.

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