# Budesonide Nanocrystal Manufacturing Using Controlled Expansion of Supercritical Solutions (CESS®).

Barry Derham[1], Jesse Heikkilä[1], Petteri Helander[1], Suvi Saarnio[1], Pablo Luis Gutierrez Carvalho[1], Elisabetta Micelotta[1]

[1]Nanoform, Helsinki, Finland

## Introduction

Poor bioavailability and low efficacy arising from poor solubility are amongst the most common reasons for drug failure [1]. An advanced approach is the generation of crystalline nanoparticles which can increase the specific surface area of API particles leading to higher dissolution rate whilst maintaining the stability of the crystalline form.

Particle production based on supercritical carbon dioxide ($scCO_2$) is an efficient, inexpensive, and ecological [2] way to produce nanoparticles by re-crystallization. In the Controlled Expansion of Supercritical Solution (CESS®) method, the nanoscale particles are produced using variable depressurization and supersaturation [3]. The core of the technology is the precise control of the nucleation and crystal growth.

The suitability of an API to be processed with CESS® can be predicted using Nanoform's cutting-edge sparse-data AI platform — STARMAP®

- Using structural information and thermal data, STARMAP® can predict a molecule's solubility in $scCO_2$ and propensity to crystallize.
- Based on this, compounds can be ranked as well as tune the manufacturing process.
- Using this approach, Budesonide was identified as an ideal candidate.

Inhaled budesonide has been used for the treatment of asthma and chronic obstructive pulmonary disease for a long time. Opportunities may arise from increasing the bioavailability and speed of effect.

starmap®
Illuminating the future of Pharma

## Analytical methods

**SEM** Stubs were sputtered with Pt and the morphology evaluated. A minimum of 200 particles from imaging 3 different points by an in-house AI software for PSD.

**XRPD** A Malvern X-ray diffractometer, equipped with a Cu anode (λ1.54 Å) in reflection mode was used to collect powder diffraction patterns.

**DSC** A Discovery X3 using temperature modulation (mDSC) was used. Thermal events are shown from the first heating cycle, Tg from the second heating cycle.

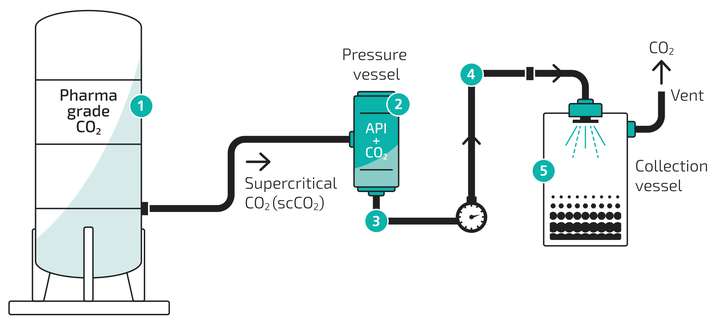
**HPLC** Waters Arc System using methods for identification, and related substances (Ph. Eur) [4].

## Materials

Poorly soluble BSC class II drug Budesonide (NewChem, Italy). $CO_2$ (purity ≥ 99.8%, AGA, Finland) was used as the solvent in particle production.

## Nanoparticle Production

A schematic of the CESS® methodology is shown in Figure 1 with the process discussed below.




1. Supercritical $CO_2$ is guided into a pressure vessel loaded with API
2. Increasing the pressure and temperature in the vessel dissolves the API in supercritical $CO_2$
3. The $CO_2$ and the API are released from the pressure vessel and the flow, pressure and temperature profiles are accurately controlled
4. The pressure and temperature is controlled to achieve a stable nucleation phase and formation of nanoparticles
5. In a collection vessel the $CO_2$ is sublimated resulting in final nanoparticles ready for collection and formulation

## Conclusions

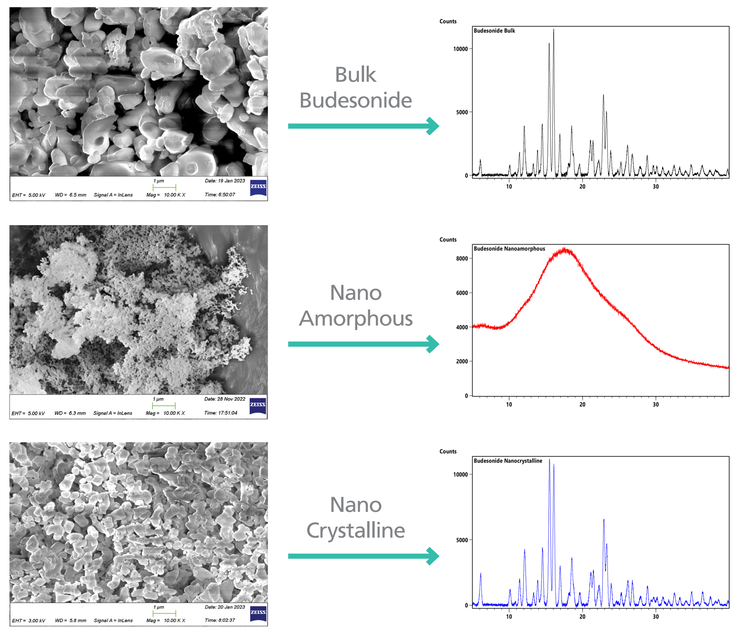
The CESS process was successful at generating either dry amorphous or crystalline nanoparticles of budesonide with a reproducible PSD span <1. The CESS process does not require the use of excipients or surfactants, thus pure drug nanoformed particles are produced.

The nanoformed material is ready to be formulated into various inhalation delivery approaches including dry powder inhalers, suspensions for nebulization and for soft mist inhalers.

Nanoform have GMP manufacturing capabilities, including highly potent compounds, for clinical-grade APIs.

## Results

Through careful control of the pressure profile during scCO2 expansion, it is possible to manipulate the crystallinity of budesonide generated from the CESS® process, without the need for additional solvents. The process is tuneable and both amorphous and crystalline material were prepared.




| Image | Dn10 | Dn50 | Dn90 | Dv50 | std | span |
|---|---|---|---|---|---|---|
| Budesonide Bulk | 403 | 748 | 1419 | 1668 | 471 | 1.4 |
| Budesonide nanocrystalline | 212 | 335 | 497 | 446 | 119 | 0.9 |
| Budesonide nanoamorphous | 61 | 90 | 141 | 125 | 32 | 0.9 |

Figure 2 -CESS® processing of bulk into nanocrystalline and nanoamorphous budesonide.

DSC thermograms demonstrated that the melting enthalpy of the nanocrystalline API has not changed in comparison with the bulk material. Nano amorphous thermograms showed a double crystallization peak at 100°C characteristic of the amorphous form (Figure 3).

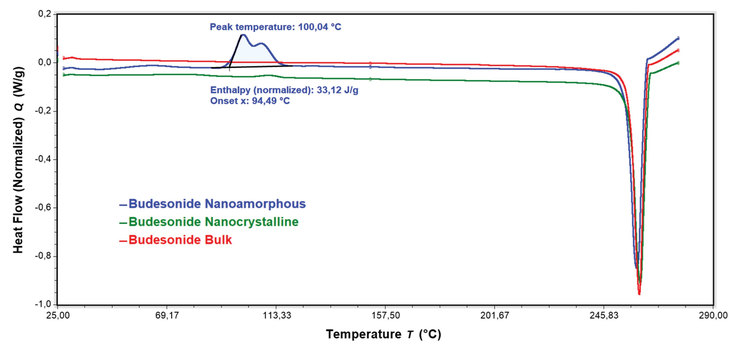



Figure 3 – DSC for bulk (Red), nanocrystalline (Green), and nanoamorphous (Blue).

The % of the two epimers of Budesonide remained unchanged (> 99.6%), for both amorphous and crystalline, compared to bulk, indicating that the CESS® process does not degrade the molecule.

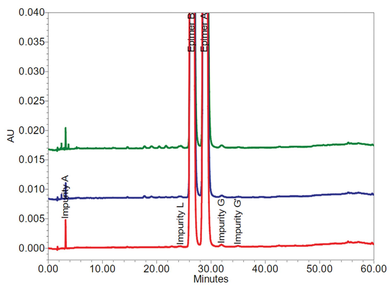



Figure 4 – HPLC chromatograms for Bulk (Red), nanocrystalline (Green), and nanoamorphous (Blue).

nanoform
small is powerful®

nanoform.com | @nanoformf

## References

[1] Williams III, R.O., A.B. Watts, A.B., Miller, D.A. (Eds.), Formulating Poorly Water Soluble Drugs, second ed., Springer, New York, 2016.

[2] Fages, J., Lochard, H., Letourneau, J.-J., Sauceau, M., Rodier, E: Particle generation for pharmaceutical applications using supercritical fluid technology. Powder Technology 2004, 141 (3): 219-226.

[3] Pessi, J, Lassila, I, Meriläinen, A, Räikkönen, H, Hæggström, E, Yliruusi, J: Controlled Expansion of Supercritical Solution: A Robust Method to Produce Pure Drug Nanoparticles with Narrow Size-Distribution. Journal of Pharmaceutical Sciences 2016, 105(8): 2293–97.

[4] European Pharmacopoeia, 10th Edition 2019, 1075: 2009-2011.