thermoscientific

Dry amorphization of itraconazole: twin-screw processing and crystallinity

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INTRODUCTION

In the development of active pharmaceutical ingredients (APIs), their bioavailability is of main concern. The metastable amorphous state of APIs can reduce the dissolution time and therefore increase bioavailability, but it needs to be stabilized by a matrix material. Polymers are predominantly used to form solid dispersions with APIs and therefore stabilize the amorphous state. Solid dispersions are mostly prepared by hot melt extrusion (HME) and spray drying. HME requires temperatures above the glass transition temperature of the polymer which often can lead to decomposition or structural change of the API, whereas spray drying requires tedious handling of a solvent.

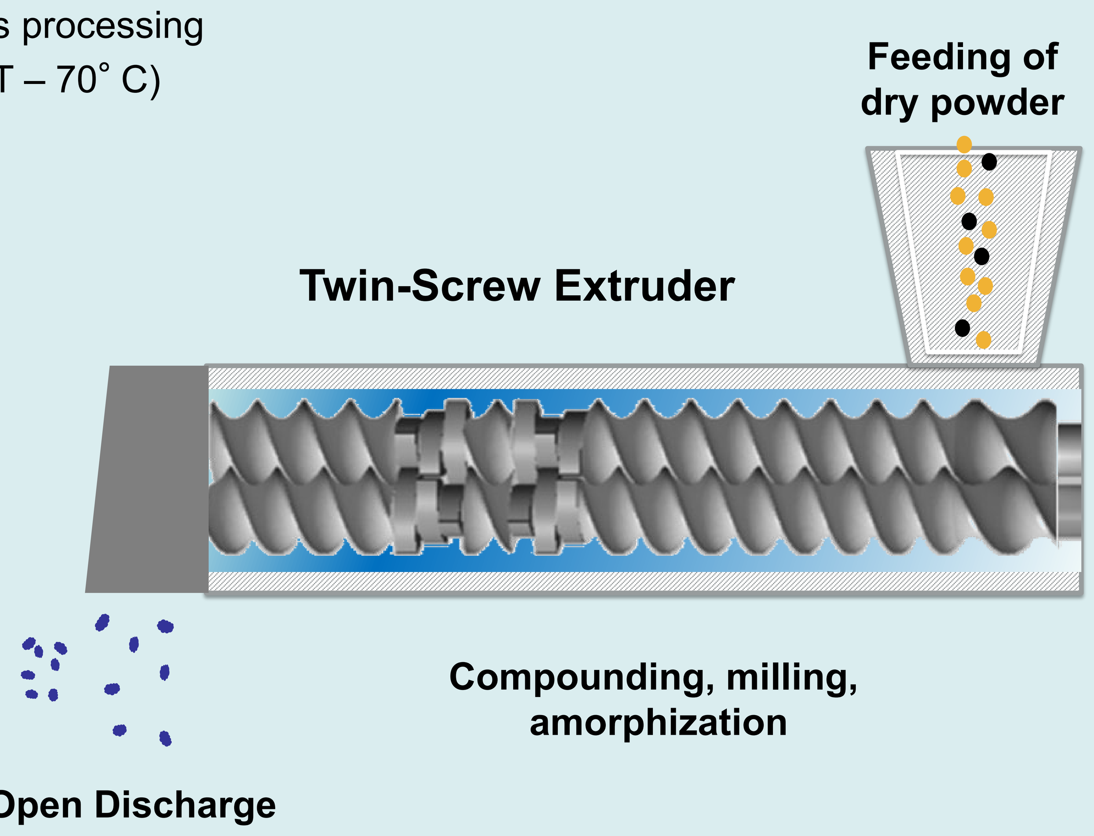
An alternative route to stabilize the amorphous state of APIs is the usage of porous silica with a well-defined pore size distribution. Recent studies [1]-[3] have shown that solvent-free ball-milling of API/porous silica mixtures at moderate temperatures can improve the dissolution rate. Nonetheless, extensive milling times and batch processing is required. Twin-screw compounding technology is a mature process which can synthesize material in a constant flow with increased reproducibility and flexibility.[4][5]

In this study, itraconazole is used as a model drug which is stabilized by a mesoporous silica matrix. Processing is carried out by a laboratory sized pharmaceutical twin screw extruder with varying screw configurations and process parameters. To analyze the quality of the processed material, powder X-ray diffraction (XRD) is used to quantify the amorphous to crystalline ratio by means of standard-less combined whole pattern refinements.

Dry Amorphization - Synthesis

Dry amorphization using continuous twin-screw technology at low temperatures

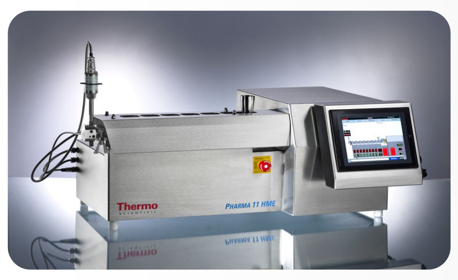
- Consistent continuous processing
- Low temperatures (RT – 70° C)
- No solvent needed



Analytical Instrumentation

Twin-Screw Extruder

- Thermo Scientific™ Pharma 11 Twin-Screw Extruder
- Residence time in extruder
- Torque of extruder
- Specific mechanical energy

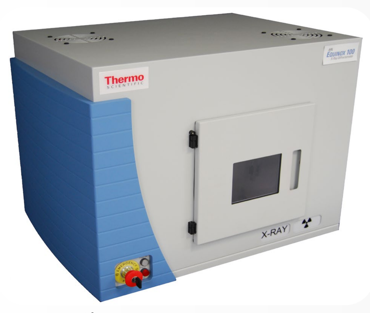


Differential Scanning Calorimetry (DSC)

- NETZSCH DSC 204F1 Phoenix (240-12-0023-L)
- Heating/cooling rate: 10 K/min
- 10 mg sample size

Powder X-RAY Diffractometer (XRD)

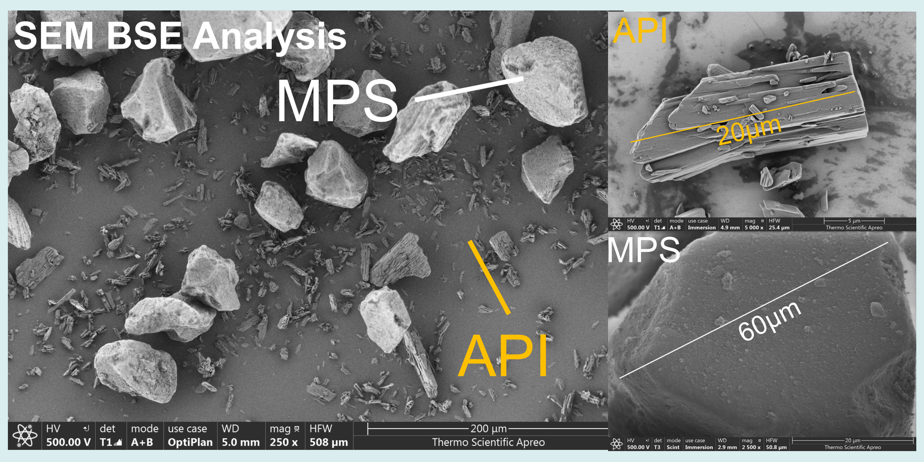
- Thermo Scientific™ ARL EQUINOX 100
- Cu Ka Radiation @ 36W Power
- Unique CPS detector technology
- 5 min measurement in reflection
- MDI JADE 2010 and ICDD PDF4+ Organic for evaluation
- Whole Pattern Rietveld Refinement to quantify phase composition (amorphous content)
- Standard-less amorphous quantification



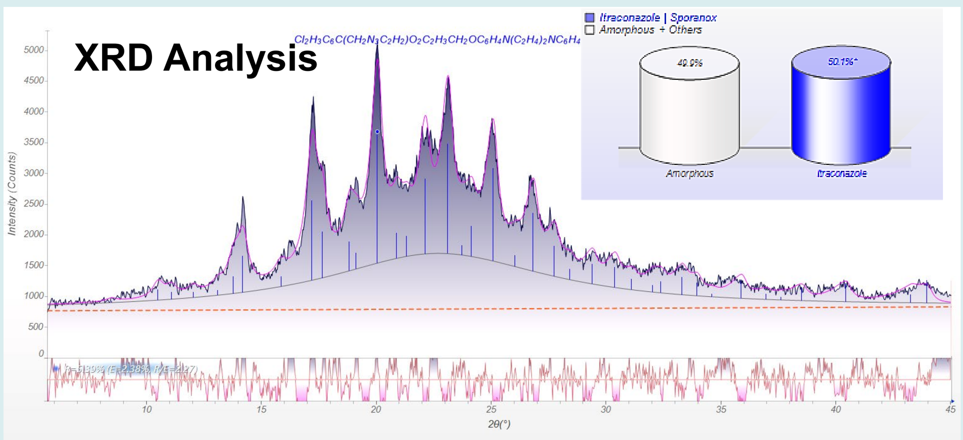
Scanning Electron Microscope (SEM)

- Thermo Scientific™ Apreo S SEM

Pre-blend analysis (1:1 ratio)

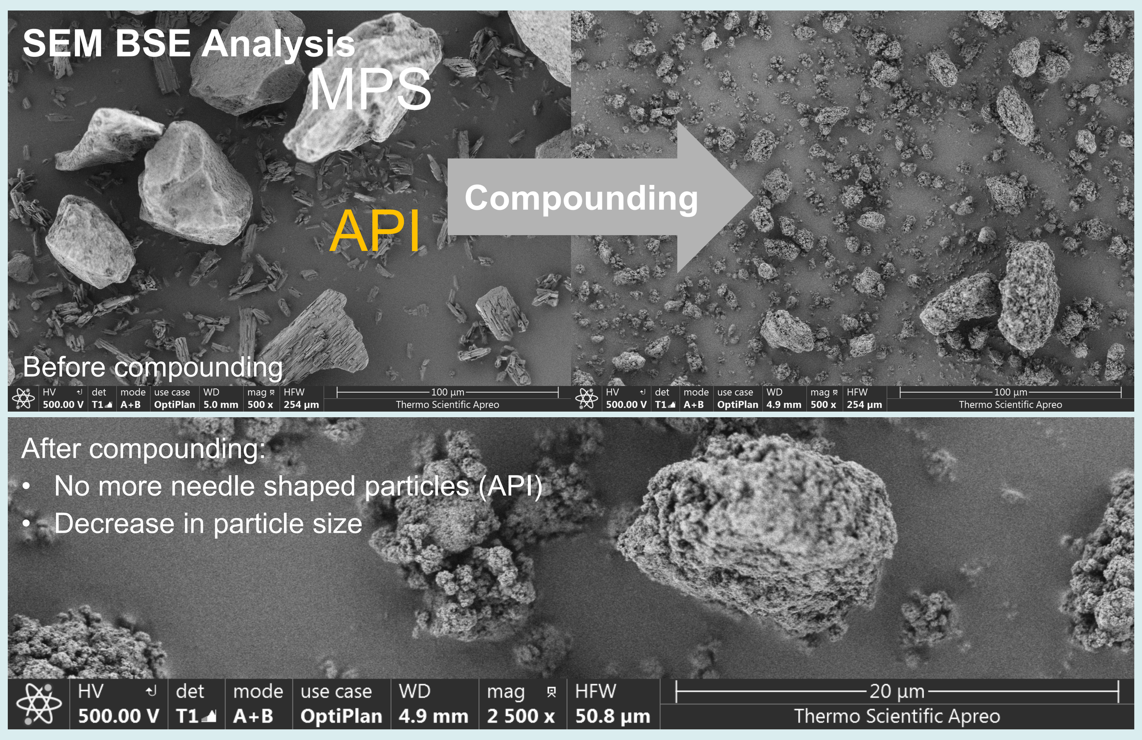


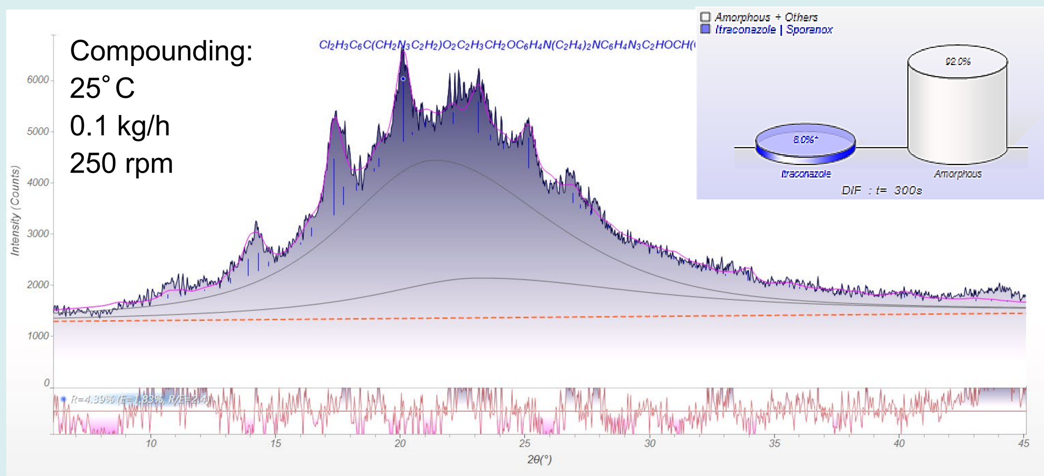
API (Itraconazole): needle shaped particles
MPS (meso-porous silica): lump like particles



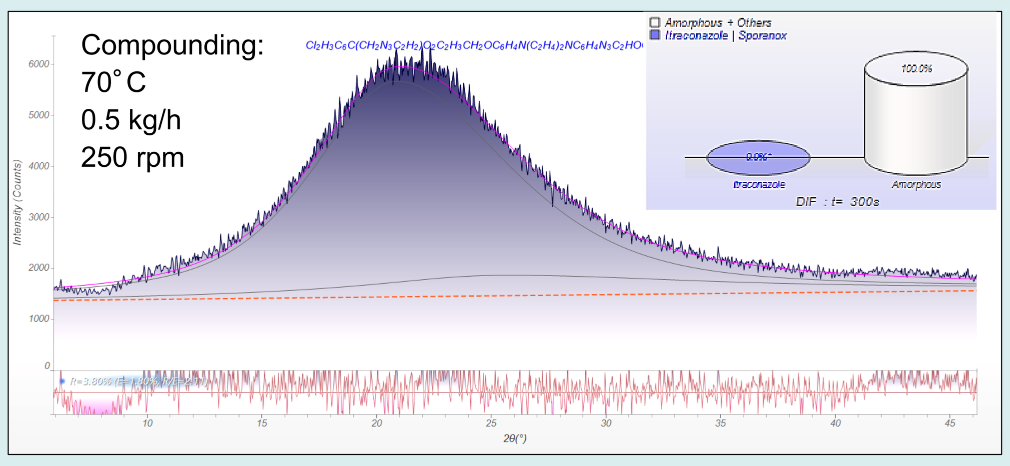
Quantitative XRD analysis of amorphous (MPS: grey) and crystalline (API: blue) components; Analysis shows 1:1 ratio and proofs the principle

Final Product analysis (1:1 ratio)

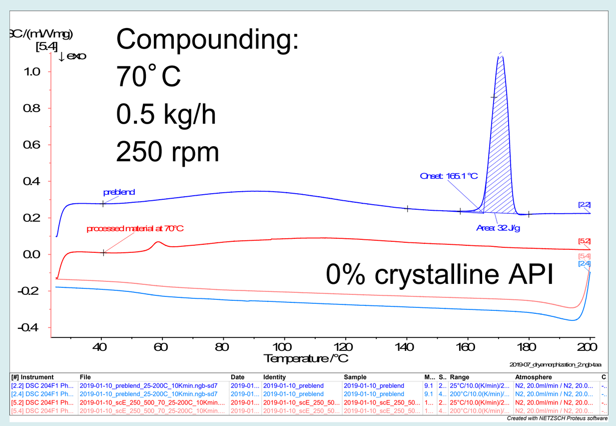




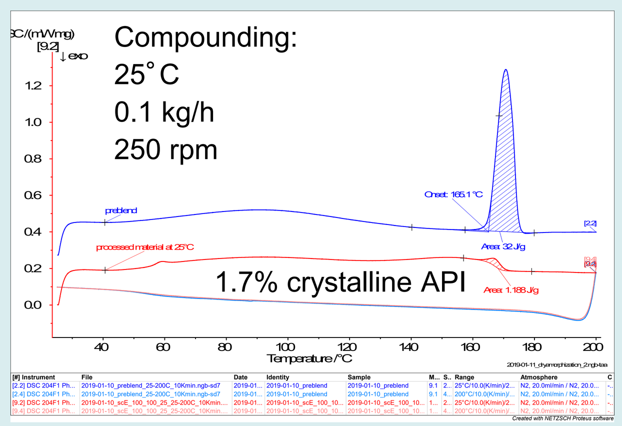
Quantitative XRD analysis of amorphous (MPS: grey) and crystalline (API: blue) components; Sample contains 8% crystalline API



Quantitative XRD analysis of amorphous (MPS: grey) and crystalline (API: blue) components; Sample is completely amorphous



DSC analysis of pre-blend (blue) and processed material (red); no melting heat in processed material indicated no remaining crystalline API phase



DSC analysis of pre-blend (blue) and processed material (red); melting heat in processed material quantifies to 1.7% remaining crystalline API phase

CONCLUSION

- Decrease in particle size after twin-screw processing
- Full amorphization succeeded at 70° C and 175° C (according to XRD and DSC analysis)
- Up to 92% of the API in a 1:1 blend with silica reached amorphous state being processed at room temperature. (according to XRD analysis); Finding supported by DSC analysis with slightly different ratio
- Proof of concept of dry amorphization with continuous twin-screw process; No need of solvents or high temperatures
- The key factors: mean residence time and specific mechanical energy

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