Chain Processing for the Production of Nanoparticles in Solid Crystalline Suspensions

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Introduction

The formulation of poorly water-soluble drugs often utilizes size reduction to submicron scale as a means to increase dissolution rate and enhance bioavailability. Solid Crystalline Suspensions (SCS) are a promising formulation technology for BCS II substances. The crystalline submicron drug particles (0.1 – 1 µm) are enclosed in a crystalline matrix of a water-soluble polyol such as Xylitol or Mannitol.

Continuous manufacturing offers many advantages over batchwise production, but is not yet readily integrated in pharmaceutical processes.

The feasibility for a continuous production of SCS is investigated by chaining extrusion and a milling step in sequence.

Materials and Methods

The following materials were used as received: Xylitol (Xylisorb 300, Roquette, Lestrem, France), Griseofulvin (Hawkins, Roseville, Minnesota, USA).

For the extrusion a ZSE 27 Maxx (Leistritz, Nuremberg, Germany) was used. Xylitol and Griseofulvin (10 w%) were pre-blended and fed to the extruder via a gravimetric feeder at 2.5 kg/h. Extrusion was carried out at 80 °C with a screw speed 250 RPM and a standard melting screw configuration. The milling process was done in a custom built batch stirred media mill with ZrO_2-Y_2O_3 grinding media (ZetaBeads Plus 0.5, NETZSCH Vakumix, Weyhe, Germany).

Griseofulvin particle size distributions were measured in a Mastersizer 3000 (Malvern Instruments, Malvern, UK) with a Hydro EV wet cell in saturated aqueous Griseofulvin solution to strip the Xylitol.

Results and Discussion

True continuous wet milling calls for the use of only one passage. In this case the product quality (here particle size distribution) is heavily influenced by the residence time [1]. The necessary grinding times for submicron particles vary depending on operating conditions, but are usually too high to make one passage operation viable.

This study showed that extrusion is a good tool to reduce milling times of SCS drastically.

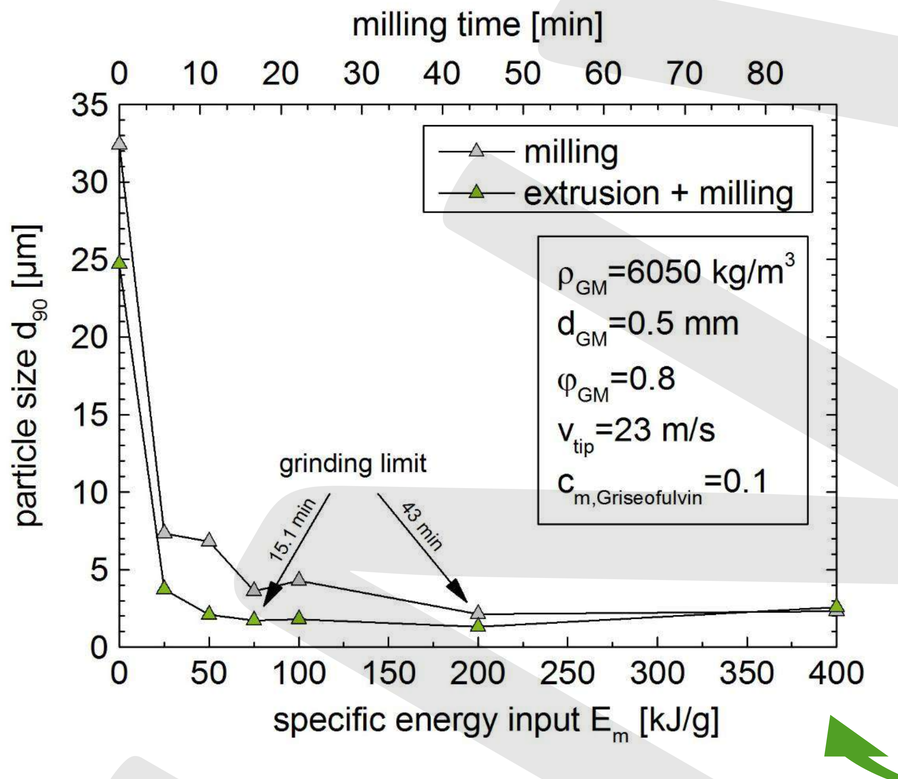

Figure 1: Comparison of API particle size (d90) in the SCS with and without the use of extrusion as a pre-processing step

The impact of extrusion on milling behavior was carried out by grinding the same pre-blended mixture with and without previous extrusion. For just milling the grinding limit was reached at a specific energy input of 200 kJ/g (43 minutes) with a size of d_{90}=2.12 µm. In case of the combined process the grinding limit was met at 75 kJ/g (15.1 min) with a slightly lower size of d_{90}=1.72 µm. An increase in specific energy input did not lead to further comminution. Generally the grinding limit with extrusion was slightly lower than without preprocessing.

The extruder and the batch mill were not directly connected, so each product was processed individually, thus only simulating an ideally chained process. Therefore the residence time in the batch mill was uniform for all stressed particles. In a truly continuously run process chain, a residence time distribution (RTD) will always lead to varying stress numbers. To account for this behavior the particle size distribution in the continuous mode can be predicted by [2]:

$$Q_{3,conti.}(d_P) = \int_0^\infty Q_{3,batch}(t, d_P) \cdot E(t)dt$$

$E(t)$ – RTD density function

Mill designs with a narrow RTD around the mean, such as an annular gap type, will decrease errors when transferring between operation modes.

$$E_m(t) = \frac{\int_0^{t_{end}} P\big(\tau(t)\big) - P_0 dt}{m_{API}}$$

E_m - specific energy input [kJ/g]
P – power draw [kW]
P_0- no load power [kW]
τ – torque [Nm
m_{API} - mass of drug [g]

CONCLUSION

Extrusion proofed viable to decrease the necessary grinding time to reach the grinding limit by 66 %. This could help setting up a true continuous production of SCS in a technical relevant scale. To transfer these results to a continuous process more accurately a unique mill design is necessary to achieve narrow RTDs.

References: [1] A. Kwade, J. Schwedes, Chapter 6: Wet Grinding in Stirred Media Mills; Handbook of Powder Technology, 12 (2007) 251-382
[2] N. Stehr, Residence Time Distributions in a Stirred Media Mill and their effect on Comminution, Chem. Eng. Process., 18 (1984) 73-83

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