MS28-2-1 Dry amorphization of itraconazole: extrusion and crystallinity
#MS28-2-1

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Abstract
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. Full amorphization is reached at 70°C, whereas up to 97% of amorphized API (1:1 blend) is achievable at room temperature, which is in good agreement to Differential Scanning Calorimetry (DSC) measurements. Additional Scanning Electron Microscopy (SEM) investigations clearly indicate a decrease in particle size of both, silica and itraconazole.

References
[1] A. Baán et al., “Dry amorphisation of mangiferin, a poorly water-soluble compound, using mesoporous silica,” Eur. J. Pharm. Biopharm., vol. 141, no. March, pp. 172–179, 2019.
[2] D. Bahl, J. Hudak, and R. H. Bogner, “Comparison of the ability of various pharmaceutical silicates to amorphize and enhance dissolution of indomethacin upon co-grinding,” Pharm. Dev. Technol., vol. 13, no. 3, pp. 255–269, 2008.
[3] F. Monsuur et al., “Solvent free amorphisation for pediatric formulations (minitablets) using mesoporous silica,” Int. J. Pharm., vol. 511, no. 2, pp. 1135–1136, 2016.
[4]C. Vervaet and J. P. Remon, “Continuous granulation in the pharmaceutical industry,” Chem. Eng. Sci., vol. 60, no. 14, pp. 3949–3957, 2005.
[5] J. Vercruysse et al., “Stability and repeatability of a continuous twin screw granulation and drying system,” Eur. J. Pharm. Biopharm., vol. 85, pp. 1031–1038, 2013