Understanding the Process-Product-Performance Interplay of Spray Dried Drug-Polymer Systems through Complete Structural and Chemical Characterization of Single Spray Dried Particles

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Purpose

Spray drying has become a commonly used technique to make amorphous solid dispersions; however, spray drying is a complex process with numerous processing variables that can potentially impact product quality. Furthermore, there exists a large gap of knowledge of this manufacturing process because the correlations between specific properties and product performance are not well understood. Physiochemical and biopharmaceutical properties of spray-dried particles can be profoundly affected by droplet size from which the particles are birthed, structural morphology/microstructure, void space, and phase behavior. Ideally, by understanding the property-performance correlation, spray-dried formulations could be developed with a rational-design approach. However, commonly used techniques for the analysis of spray-dried particles focus on the bulk sample and lack the required resolution needed to understand the scientific link between the processing conditions and the resultant particles. The current study highlights the utility of one high-resolution imaging technique; focused-ion scanning electron microscopy (FIB-SEM).

Methods

To interrogate the utility of FIB-SEM in characterizing the morphology and chemical composition of single-particle amorphous solid dispersions (ASDs), a model system of felodipine as the API, and polyvinyl pyrrolidone (PVP) as the polymer was selected. Amorphous solid dispersions were prepared by first completely dissolving felodipine in methanol, then PVP-K30 was added to the felodipine solution, and mixed using a magnetic stir bar until completely dissolved. Two solutions with 53% and 70% (w/w solids basis) drug loading, but with the same total solids loading of 2.47% (w/w) in solution were prepared. As well as one solution with 0.63%, (w/w) solids loading, but with a drug loading of 53% (w/w solids basis). The solutions were spray dried on the 4M8-TriX spray dryer (ProCepT nv, Zelzate, Belgium). The bulk properties of resultant particles were analyzed with powder X-ray diffractometry (PXRD) and modulated differential scanning calorimetry (mDSC) to detect the presence of crystallinity and the homogeneity of particles, respectively. Furthermore, to analyze the physical morphology and chemical composition of single particles, FIB-SEM coupled with energy dispersive X-ray spectroscopy (EDS) was utilized.

Results

Within a single spray drying batch, individual particles exhibited different phase behavior as a function of particle size. Larger particles showed notable amorphous-amorphous phase separation while smaller particles showed uniform composition. The morphology of particles was also found to be a function of particle size. Larger particles were consistently more porous in nature compared to smaller particles.

Conclusion

Microanalysis of individual particles, especially multi-component single phase systems with FIB-SEM and EDS provided excellent insight into the mechanism of particle formation and the relationship between particle structure and chemical composition as it allows for direct observation of single particle surface and internal morphologies and phase behavior in great detail. The data presented shows amorphous-amorphous phase separation on single spray dried particles. Most strikingly, the differences in phase behavior that can be observed as a function of particle size, even within a single spray drying process condition. The observed differences in the compositional heterogeneity of different spray dried particles as a function of size are interpreted via theoretical arguments based on the Peclet number, the ratio of the evaporative flux of the solvent to the diffusive flux of the drug and the polymer within the droplet.