Investigation of Mixing and Segregation of Ordered Mixtures for Dry Powder Inhaler Formulations

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The purpose of the current study is to guide the pharmaceutical industry towards rationally choosing blenders and processing conditions for making ordered mixtures based on relevant criteria. Ordered mixtures were formed in a high shear mixer (HSM) and in a low shear double cone blender (DCN). Mixing patterns were systematically investigated using experiments and numerical models. 6 samples were taken at different spatial locations within the blenders and analyzed to monitor the fraction of particles below 10 μm in size using a Malvern Mastersizer 2000E fitted with a dry Scirocco dispersion unit operated at a pressure of 4 bars. The performance of blenders was tested with respect to the following criteria: time, demixing tendency, press-on-forces, blend tribocharging and wall sticking of the drug. In addition, process variables (rotation speed, loading configuration and fill volume) were investigated as a function of time. Discrete Element Method (DEM) was used to simulate the powder flow within the blenders. The cohesive and adhesive forces were included through dimensionless bond numbers, which represent the ratio of cohesive force to particle weight. Increased rotation speed and a central loading configuration were associated with the fastest mixing, but increased speed was also associated with a greater tendency to demix and wall adhesion of API. Ordered mixtures from DCN were formed after a much longer time, but had a lower tendency to demix. Press-on forces of the blend from both the blenders were not differentiable. DEM simulations revealed that HSM achieved greater velocities but produced lower chaos, while the inverse was true for DCN. DCN was predicted to form ordered mixtures quickly given the adhesion between the drug and carrier was strong. The effect of material adhesion was not pronounced for HSM. HSM was also predicted to approach the theoretical limit of ideal ordered mixture in contrast to DCN.