Understanding Particle Formation in a Moving Droplet using the Classical Theory of Nucleation and Diffusion-based Growth Mechanism: A Modeling Approach

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ABSTRACT

Particle size reduction of the active pharmaceutical ingredients (APIs) in the range of 1-5 µm is required for efficient drug delivery through the nasal route. The traditional micronization techniques such as jet milling, spray drying and liquid antisolvent recrystallization exist to produce the particles in this size range. However, these techniques have many disadvantages such as irregular particles, broad particle size distribution, chemical and thermal degradation. Supercritical fluid-based micronization techniques have been proved as a promising technology to produce spherical particles in this size range. In this work, a model is developed to predictthe particle size distribution of API recrystallized by a supercritical antisolvent recrystallization process. Rifampicinis considered a modal API to be recrystallized. In this process, the API is first dissolved in dimethyl sulfoxide and this solution is sprayed into a precipitator. The precipitator has carbon dioxide at supercritical conditions i.e., above its critical temperature and pressure. Supercritical Carbon dioxide acts as an antisolvent as rifampicin is not soluble in it. Diffusion of carbon dioxide into solution droplet decreases the solubility of rifampicin in dimethyl sulfoxide and the crystallization process starts. Primary nucleation and diffusion-based growth mechanism are considered to calculate average particle size and particle size distribution. This model is solved in MATLAB 7.1 and the trend of particle size distribution predicted by the model is found to be similar to particle size distribution by experiments.

Keywords: Supercritical carbon dioxide; nucleation; growth; crystallization; particle size distribution

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