Controlled Liquid Antisolvent Precipitation of Poorly Water Soluble Drugs using Rapid Mixing Device

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Nano/micro-particulate formulation is a promising way to improve bioavailability of poorly water soluble BCS class II drugs. Among the various techniques available for production of ultra-fine particles, liquid antisolvent (LAS) precipitation offers flexibility to control the particle size and distribution by manipulating physicochemical properties of solution and antisolvent phases using the additives. Particle formation by LAS involves two steps, namely the mixing of solution-antisolvent streams to generate supersaturation and the precipitation (which involves nucleation and growth by coagulation and condensation) of the particles. Thus, there are two main time scales associated with it, mixing time (τ_{mix}) and precipitation time or induction time ($\tau_{precipitation}$). Dimensionless Damkohler number (*Da*) is the ratio of τ_{mix} and $\tau_{precipitation}$. Value of $Da > 1$ implies the mixing controlled process whereas $Da < 1$ implies that the precipitation step controls the process. Under a condition of $Da < 1$, mixing time is significantly less; mixing is uniform, and particle size is not affected by the mixing conditions. This produces rapid and uniform supersaturation and results in the precipitation of ultrafine particles. Thus, it is necessary to reduce τ_{mix} and increase $\tau_{precipitation}$ in order to keep $Da < 1$. In this work, we demonstrate the use of a T-shaped mixing device to precipitate ultra-fine particles. The greater control over particle size and its distribution has been achieved through enhanced micromixing and stabilization using various polymers and surfactants. Analysis of micro-mixing and stabilization has also been carried out to identify the extent of influence of above two steps and develop a methodology to control particle size and size distribution. The methodology developed using a T-shaped micro-mixer, has been illustrated for precipitation of ultra-fine particles of multiple APIs in the size range of 100 nm – 10 μm as a function of process parameters.