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Controlled liquid antisolvent precipitation using a rapid mixing device

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ABSTRACT

Particle formation by the liquid antisolvent (LAS) process involves two steps: mixing of solution–antisolvent streams to generate supersaturation and precipitation (which includes nucleation and growth by coagulation and condensation) of particles. Uniform mixing conditions ensure rapid and uniform supersaturation, making it a precipitation controlled process where the particle size is not further affected by mixing conditions and results in precipitation of ultra-fine particles with narrow particle size distribution (PSD). In this work, we demonstrate that the use of an ultrasonically driven T-shaped mixing device significantly improves mixing of solution and antisolvent streams for precipitation of ultra-fine particles in a continuous operation mode. LAS precipitation of ultra-fine particles of multiple active pharmaceutical ingredients (APIs) such as itraconazole (ITZ), ascorbyl palmitate (ASC), fenofibrate (FNB), griseofulvin (GF), and sulfamethoxazole (SFMZ) in the size range 0.1–30 μm has been carried out from their organic solutions in acetone, dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), and ethanol (EtOH). Classical theory of homogeneous nucleation has been used to analyze the result, which suggests that higher nucleation rate results in finer particle size. Interestingly, experimental determination of degree of supersaturation indicates that higher supersaturation does not necessarily result in higher nucleation rate and nucleation rates can be correlated to solvent polarity.

1. Introduction

A significant proportion of the Biopharmaceutics Classification System—BCS class II drugs in the market are poorly soluble in water and it is generally accepted that use of nano/micro-particles in the formulation is a promising way to improve bioavailability of poorly water soluble class II drugs (Amidon et al., 1995; Lipinski, 2002; Noyes and Whitney, 1897). Reducing drug particle size speeds up rate of dissolution by enlarging the surface area. The Gibbs–Thomson equation Krishnamachari et al. (1996) provides a connection between bulk solubility (C_∞) and solid–liquid interface (C_r), indicating how solubility can be improved using the antisolvent technique by reducing particle radius in order to make the ratio of C_r to C_∞ close to one:

$$\ln\left(\frac{C_r}{C_\infty}\right) = \frac{2\sigma V_m}{RTr} \quad (1)$$

Here C_r and C_∞ (mg mL^{-1}) are solubility of a particle of size r and bulk solubility or solubility of a particle with large flat surface, respectively, σ is the interfacial energy (J/m^2), R is in J/mol K, r is the particle radius (m), T the solution temperature (K), and V_m the molar volume of a particle of size r (m^3/mol).

Among the various techniques available for production of ultra-fine particles, liquid antisolvent (LAS) precipitation offers flexibility to control particle size and distribution by manipulating physicochemical properties of solution and antisolvent phases using additives (Horn and Rieger, 2001; Myerson, 2002; Ventosa et al., 2005; Dalvi and Dave, 2009; Zhang et al., 2009). On the other hand, the use of T-mixers has been shown to enhance micromixing and to provide nanoparticles through reactive crystallization (Schwarzer and Peukert, 2004), which is a promising and commercially relevant method for particle formation, but not well-explored for the LAS process. Our study therefore employs a T-mixer for LAS precipitation with a provision to use ultrasound in the mixing zone. Although the T-mixer has not been extensively studied for LAS precipitation of nano and sub-micron particles, several studies have used variations of the T-mixer (Johnson and Prud'homme, 2003a; Zhao et al., 2007) to produce stable particles as well. The T-mixer removes the technological challenges associated with impinging jets such as alignment of nozzles and permits introduction of ultrasound, which results in a compact and continuous mode device. In a T-mixer, streams of drug solution and antisolvent collide in a mixing zone, where high supersaturation is achieved. The generation of high supersaturation is further improved by employing ultrasonication, wherein the metastable region is decreased (Lyczko et al., 2002; Guo et al., 2006). Enhanced mixing conditions help generate a sufficiently large number of these nuclei to limit growth rates (Dalvi and

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Dave, 2009; Kumar and Prud'homme), and therefore result in the precipitation of ultra-fine particles.

The current paper illustrates the use of T-mixer as a rapid mixing device in the presence of ultrasound to produce aqueous suspensions of ultra-fine active pharmaceutical ingredient (API) particles. Such aqueous suspensions of fine API particles can be used in multiple downstream processes such as in liquid gel-caps, formation of edible films via addition of bio-compatible polymers, or spray-dry granulation and in all cases, may help reduce problems associated with the handling and containment of very fine, dry API particles. In the following, first the estimates of mixing time, precipitation time, and Damkohler number are presented in order to evaluate mixing efficiency of T-mixer with and without ultrasound; next, the performance of a T-mixer with ultrasound is evaluated for production of ultra-fine particles of several candidate APIs. The classical nucleation theory has then been utilized to analyze kinetic and thermodynamic driving forces of LAS. Together, these studies allow for a better understanding of antisolvent crystallization processes utilizing a rapid mixing device.

2. Theoretical

2.1. Characterization of ultrasonically driven T-mixer

As stated earlier, particle formation by LAS involves mixing of solution–antisolvent streams to generate supersaturation and precipitation of particles. Thus, there are two main time scales associated with it; mixing time (τ_{mix}) and precipitation time ($\tau_{precipitation}$), which is also called the induction time; $\tau_{precipitation}$ refers to time scale of physical changes incurred during phase shift, which are nucleation and growth. The ratio of τ_{mix} to $\tau_{precipitation}$ is the dimensionless Damkohler number (Da):

$$Da = \frac{\tau_{mix}}{\tau_{prec}} \tag{2}$$

A value of $Da > 1$, implies a mixing controlled process whereas $Da < 1$ implies that the precipitation step controls the process. Therefore, if the device mixes the solvent and antisolvent streams optimally, the Damkohler value shifts to $Da < 1$, subsequently driving the process to yield ultra-fine particles (Zhao et al., 2007).

2.1.1. Mixing and precipitation time scales

Three time scales are recognized when mixing is considered as the rate limiting step in pharmaceutical crystallizations processes: macroscale, mesoscale, and microscale. Macromixing has been shown to have no significant influence on final product distribution (Torbacke and Rasmuson, 2001). Therefore, the overall mixing scale is mainly influenced either by mesomixing or micromixing and is described as follows:

$$\tau_{mix} = \tau_{meso} + \tau_{micro} \tag{3}$$

$$Q_m = \frac{\tau_{meso}}{\tau_{micro}} \tag{4}$$

Q_m can also be predicted as follows:

$$Q_m = \frac{Eq_o}{uD_t} \tag{5}$$

$$D_t = \frac{(0.1k^2)}{\varepsilon}, \quad \tau_{meso} = \frac{q_o}{uD_t}, \quad \tau_{micro} = \frac{1}{E}, \quad E = 0.058\left(\frac{\varepsilon}{\nu}\right)^{0.5} \tag{6}$$

where D_t represents the turbulent diffusivity (Baldyga et al., 1995), u is the solution velocity, q_o is the volumetric flow rate, ν the kinematic viscosity, and ε the energy dissipation rate (Torbacke and Rasmuson, 2001; Baldyga et al., 1995). Q_m indicates the relative degree of exchange of material between eddies in a suspension (Vicum et al., 2004), and contributions of mesomixing and micromixing to the redistribution of material can be evaluated using Q_m.

When

$$Q_m < 1, \quad \tau_{mix} = \tau_{micro} \tag{7}$$

$$Q_m > 1, \quad \tau_{mix} = \tau_{meso} \tag{8}$$

In cases where Q_m is large and greater than 1, mesomixing controls and if Q_m is small and lower than 1, micromixing controls. Consequently, if mesoscale mixing controls the mixing rate, shear forces (viscous) are the main components controlling the process. At higher intensity, mesomixing significantly controls mixing up to eddy scales slightly higher than Kolmogorov scales. If micromixing is the governing phenomenon, molecular exchanges are the main contributors to mass transfer (Baldyga et al., 1995). This being intrinsic to the system, it is rather difficult to control molecular interactions. However, it is possible to introduce a certain external force as ultrasonic waves that can improve micromixing.

The precipitation time can be approximated using the following correlation (Baldyga et al., 1995):

$$\tau_{precipitation} = \left(\frac{6n^* d^2}{D_{AB} \ln S}\right) \tag{9}$$

where D_{AB} is the diffusion coefficient of the solute, $\ln S$ the supersaturation ratio, d the mean particle diameter, and n^* the number of molecules present in the solute.

2.1.2. Energy input

Several studies have been conducted on the characterization of energy contributions in rapidly mixing devices (Johnson and Prud'homme, 2003b; Panagiotou et al., 2009; Siddiqui et al., 2009). It was established that pressure drop does not constitute an immense contribution vis-à-vis the dissipation medium for mixing. Consequently, pressure drop is ignored (Mahajan and Kinvan, 1996) for the estimation of energy input to T-mixer, and hence we can use the following correlation for power dissipation P:

$$P \propto [(mu)_1 + (mu)_2 + US] \tag{10}$$

Eq. (10) shows that the power input for size reduction in a T-mixer is equivalent to kinetic contributions plus variations in waves added through ultrasonication.

2.2. Thermodynamic and kinetic aspects of nucleation

Crystallization processes are thermodynamically driven and the kinetics of nucleation is significantly influenced by parameters such as equilibrium solid solubility (and hence supersaturation), solid–liquid interfacial energy, and diffusivity. According to the classical theory, nucleation rate (J) is obtained from the following correlation (Lyczko et al., 2002; Guo et al., 2006):

$$J = J^0_{hom} \exp\left(\frac{-16\pi}{3}\left(\frac{\sigma}{kT}\right)^3 \left(\frac{1}{C_c N_A}\right)^2 \left(\frac{1}{\ln^2 S}\right)\right) \tag{11}$$

$$J^0_{hom} = 1.5 D_{AB} (CN_A)^{2.33} \left(\frac{\sigma}{kT}\right)^{0.5} \left(\frac{1}{C_c N_A}\right) \tag{12}$$

where

$$S = \frac{C}{C_{eq}} \tag{13}$$

The diffusion coefficient D_{AB} can be estimated as follows (Choi et al., 2002):

$$D_{AB} = 8.98 \times 10^{-8} \left(\frac{V_A}{V_B^2}\right) \left(\frac{P_B}{P_A}\right)^{0.6} \left(\frac{T}{\eta_B}\right) \tag{14}$$