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Nanoparticle stability: Processing pathways for solvent removal

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ABSTRACT

Processing of hydrophobic organic compounds into nanoparticle form by rapid precipitation requires the use of organic solvents in which the compounds are initially dissolved. Mixing with an antisolvent induces supersaturation, nucleation and particle growth. In most cases the nanoparticle is to be dispersed in an aqueous phase and so the antisolvent is water and the organic solvent is a water-miscible organic. Ultimately the organic solvent must be removed because its presence either has toxicological consequences or it reduces particle stability against Ostwald ripening. Dialysis is commonly used to remove organics; however, the process is slow and costly. We present an efficient and scalable process of solvent removal based on flash evaporation. The non-ideality of the water:tetrahydrofuran (THF) activity coefficient makes the process especially effective. The results are compared against phase equilibria calculations and two flash stages are shown to reduce THF concentrations by over 95%, and bring the residual solvent concentration within acceptable limits for drug applications.

1. Introduction

Hydrophobic drug compounds account for 40% of the new drug candidates under FDA review (Lipinski, 2002). Considerable effort has been directed at increasing the bio-availability of these hydrophobic compounds by creating nanoparticle formulations with high surface-to-volume ratios. Conventional techniques to form nanoparticles include slow anti-solvent addition followed by dialysis (Allen et al., 1998; Kim and Lee, 2001), solvent evaporation (Shuai et al., 2004) and emulsification followed by solvent stripping (Kwon et al., 2001; Song et al., 1997). Rapid precipitation from an organic solvent into an aqueous anti-solvent has proven an attractive processing scheme for laboratory studies (Horn and Rieger, 2001; Hu et al., 2004; Johnson and Prud'homme, 2003a,b) as well as for large scale operations (Luddecke and Schweikert, 1999). In all of these approaches, organic solvents must be employed in the processing to solubilize the active compound, then the organic solvents must be removed (Liu et al., 2007). Conventional processes such as dialysis require hours or days and are relatively expensive (Kim and Lee, 2001; Shuai et al., 2004), and lyophilization can be problematic for relatively high concentrations of organic solvent (Vandervoort and Ludwig, 2002).

In this note we demonstrate the use of flash evaporation to rapidly remove tetrahydrofuran (THF) from a nanoparticle dispersion produced by Flash NanoPrecipitation (Johnson and Prud'homme, 2003a,b). Flash evaporation can be easily scaled from laboratory preparation of research samples to large-scale production; and it enables rapid solvent removal to enhance nanoparticle stability. We demonstrate the increased particle stability that comes from removal of the organic solvent from the aqueous phase. The process can be simulated using Aspen software and the agreement between the simulation and the experimental results is quite good. A two-stage flash process brings the THF concentration below limits specified by the FDA for drug applications (Dwivedi, 2002).

Flash NanoPrecipitation is the process we have developed that is based on rapid micro-mixing of two streams: solvent and anti-solvent. The solvent stream is composed of an amphiphilic block copolymer and hydrophobic drug dissolved in water-miscible organic solvent such as THF, methanol, dimethyl sulfoxide or dimethylformamide. For vacuum stripping, a solvent more volatile than water, such as methanol or THF, is required. The strong non-ideality in the THF–water vapor–liquid equilibria and the solvency of THF for many organic compounds makes it an especially attractive solvent for flash evaporation. Water is generally used as the anti-solvent. The mixing is carried out in a Multi-Inlet Vortex Mixer (MIVM) (Liu et al., 2008) to yield a supersaturation as high as 1000 in time scales on the order of milliseconds. Particle formation depends on tuning the kinetics of nucleation of the solute to that of the block copolymer self-assembly. The process effectively controls the particle size and produces particles with a narrow particle size distribution (Johnson and Prud'homme, 2003a). Particle size can be tuned by controlling the extent of supersaturation and it has been observed that

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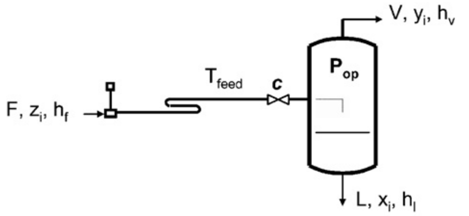

Fig. 1. Schematic representation of Flash evaporation process. "P_{op}" is the operating pressure of the vacuum chamber and "c" represents the throttling valve.

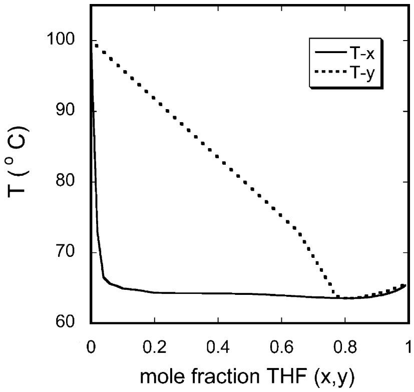

Fig. 2. The *T-x,y* diagram for water/THF at atmospheric pressure. *x* and *y* are the mole fractions of THF in liquid and vapor phase, respectively.

increasing the extent of supersaturation (i.e. increasing the ratio of water to organic solvent) leads to smaller particles (Liu, 2007). The process necessarily results in a final product stream that contains nanoparticles in an aqueous phase containing between 10% and 50% (by vol) organic solvent.

For nanoparticles the presence of the solvent increases the solubility of the active in the aqueous phase and accelerates the process of Ostwald ripening—the coarsening of the particle size distribution caused by the dissolution of smaller particles and growth of larger particles, which is driven by the dependence of solubility on particle radius (Davis et al., 1981; Hoang et al., 2004; Lifshitz and Slyozov, 1961; Liu et al., 2007). Liu et al. studied the effect of β-carotene solubility on Ostwald ripening rates in THF–water solutions. Changing the solvent:non-solvent ratio (THF:water) from 1:4 to 1:20 (vol:vol) reduced the solubility of β-carotene by a factor of 40 and reduced the average particle growth rate by a factor of 10 (Liu et al., 2007). Consequently, it is imperative to remove the organic solvent as rapidly as possible for stable nanoparticle formulation.

2. Solvent removal by flash evaporation

Flash evaporation (McCabe et al., 2004) involves partial vaporization of a preheated liquid stream by a sudden reduction in pressure (Fig. 1). As the preheated liquid stream is sprayed inside a vacuum chamber the organic solvent is removed more efficiently than a simple vacuum evaporation because of the high surface area and higher temperature. Moreover, flash evaporation results in the cooling of residual liquid, shortening the time over which suspension is at higher temperature and hence prevents instability caused by higher solubility of solute at high temperature. The vapor–liquid equilibrium for the water–THF mixture shows a high degree of non-linearity in its *T-x,y* behavior (Fig. 2) which means that the mole fraction of THF in the vapor is much higher than the ratio in the liquid phase. This enhances the separation. The governing equations for flash evaporation are the traditional mass and energy balances:

Overall material balance:

$$F = V + L \tag{1}$$

Material balance for component *i*:

$$Fz_i = Vy_i + Lx_i \tag{2}$$

Enthalpy balance:

$$Fh_f = Vh_v + Lh_l \tag{3}$$

The mole fractions of component *i* in the vapor and liquid stream are obtained by numerical solution of Eqs. (1)–(3). ASPEN simulation software (ASPEN Technology, Inc.) provides the required thermodynamics data to determine the enthalpies and equilibria for the water–THF system.

3. Experimental

Poly(ethylene glycol)-*b*-polystyrene, PEG-*b*-PS, (3K-*b*-1K) (90 mg) was dissolved in THF (5 mL, HPLC grade). The model hydrophobic compound, β-carotene (90 mg) was dissolved in THF (5 mL). Both solutions were mixed to give 1 wt% of PEG-*b*-PS and β-carotene in THF. The organic solution was fed (12 mL/min) along with water (three streams with 36 mL/min each) into a four-stream MIVM (Liu et al., 2008). The nanoparticle suspension obtained here will be referred to as *NP*.

Flash evaporation: The nanoparticle suspension, *NP*, was preheated to 45 °C. The heated solution was fed to a vacuum chamber operating at 1.72 kPa. Due to the limited capacity of the vacuum pump the pressure rose to 7.79 kPa during the flash step. The residual liquid was collected and will be referred to as *NPF*1. The residual liquid was fed again to the chamber operating at the pressure of 1.72 kPa. The feed temperature for the second stage was 35 °C and pressure in the chamber rose to 6.14 kPa. The residual liquid, referred to as *NPF*2, was collected and filtered through 0.45 μm PVDF membrane for particle size analysis.

Dialysis: Another batch (20 mL) of nanoparticle suspension, *NP*, was dialyzed against 1000 mL Milli-Q water using a Spectra/Por (Spectrum Laboratories, Inc.) dialysis membrane with molecular weight cut-off of 6–8K. The sink condition was maintained by replacing water frequently (every 15 min for first 2 h and once after 12 h) and the sample was analyzed after 2 days. This dialyzed solution will be referred to as *NPD*.

4. Results and discussion

Table 1 gives the ASPEN calculated values of solvent-removal for single stage evaporation at different operating conditions. A higher feed temperature and lower operating pressure enhance the removal of THF from the feed. Using one stage of evaporation for even a very high vacuum (0.69 kPa) and a higher feed temperature of 55 °C still results in a residual THF concentration of 0.7 wt% (greater than FDA approved limit of 0.5 wt% THF).

4.1. Correlation of experimental and ASPEN results

A water–THF mixture was processed by flash evaporation and the residual THF concentration was determined by gas chromatography (GC). The sample feed was prepared with the same composition ($x_{THF} = 0.025$) as the nanoparticle suspension obtained from the vortex mixer (THF:water = 1:9, volume basis). For single stage