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Antisolvent crystallization of carbamazepine from organic solutions

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ABSTRACT

Carbamazepine was crystallized from organic solutions using an antisolvent crystallization technique. Ethanol was used as a solvent for the carbamazepine and distilled water was used as an antisolvent. The carbamazepine was dissolved in the solvent, and the drug solution was injected into the antisolvent causing the particle precipitation. During the crystallization experiments, the effects of the process parameters such as solution concentration, temperature, injection rate of the solution, and the presence of ultrasound, were investigated. An analysis of the produced particles showed that external characteristics such as particle size and its distribution were a strong function of the process parameters, while the internal structures such as crystallinity and thermal stability were nearly unaffected. Smaller particles were obtained when solutions with high drug concentrations were used. Higher temperature resulted in larger crystals. Particle size was also influenced by the injection rate of the drug solutions. Carbamazepine particle size was significantly reduced when the ultrasonic wave was selectively applied.

Keywords: Antisolvent; Carbamazepine; Crystallization; Particle size; Ultrasound

1. Introduction

Antisolvent crystallization is one of the separation and purification methods that can be substituted for cooling- or evaporation-based crystallization techniques. Like the other crystallization methods, the antisolvent crystallization produces crystals from solutions and controls the crystalline properties such as particle size and external habits. The principle of antisolvent crystallization starts from the selection of suitable solvents and antisolvents for a crystallizing compound, and the crystallization takes place upon the mixing of the two liquid media. The major intention for the antisolvent crystallization is to reduce the solubility of the solvent toward the dissolved compounds and to change the solubility dependency on temperature in order to facilitate crystallization from solutions (Weingaertner et al., 2000).

Antisolvent crystallization has been utilized to change the solid-state properties of pharmaceutical substances including the modification of crystal form and particle size distributions. Antisolvent crystallization is a material (solvent)-induced crystallization process in which any heating and cooling steps are excluded. Therefore, this technique is suitable for the crystallization of heat sensitive substances such as explosives, polymers and pharmaceutical compounds. Recently, two types of antisolvents (gas and supercritical fluids) have been popularly employed to crystallize drugs and polymers (Reverchon et al., 2009; Salmaso et al., 2009). In these studies, a gaseous media (carbon dioxide) was selected as an antisolvent, which required using expensive high-pressure equipment. Therefore, it is worth investigating the use of a liquid media as an antisolvent because the experiments can be conducted under ambient conditions. Indeed, water can be successfully used as an antisolvent because of its low solubility toward most drug compounds and the relatively high miscibility with some polar solvents such as alcohols. When water is used as an antisolvent, the experiments can be performed without using heavy duty equipment and therefore, additional experimental variables, such as ultrasonic waves, can be easily applied during the crystallization process. In fact, the presence of ultrasound during the crystallization process affects the rate of nucleation and crystal growth and can alter the physical properties of the resulting particles. Crystallization under the influence of ultrasound is generally called sonocrystallization and this technique is primarily applied to

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