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Precipitation of Griseofulvin Via Impinging Jets in Stirred-Tank Reactors

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Griseofulvin, a commercially available active pharmaceutical ingredient (API), was precipitated here using a solvent/anti-solvent approach in an impinging jet system placed within a stirred-tank reactor. Griseofulvin was dissolved in an acetone solution, and an aqueous solution containing a polymer (HPMC) and a surfactant (SDS) was used as anti-solvent. The impinging jet mixer consisted of two jet nozzles arranged diametrically opposed to each other and facing each other. The jet nozzles were organized in a submerged arrangement within the stirred-tank reactor. Sonication was also introduced at the point of impingement by way of a sonication probe. The effect of a number of operating parameters such as sonication power and angle of impingement of the two jets on the resulting particle size distribution and crystal structure was studied. The particle size distribution was measured using a laser diffraction particle size analyzer, and the precipitated griseofulvin crystals were analyzed using Scanning Electron Microscopy (SEM) and X-ray Diffraction (XRD) to obtain an image of the crystal shape and structure. Crystals with smaller mean particle sizes were produced when the two jets were oriented 180 degrees apart and pointed directly at each other. The introduction of ultrasonic power at the impingement point resulted in markedly smaller mean particle size and a tighter particle size distribution. The results were typically highly reproducible. The crystal structure was unaffected by different operating conditions, as shown by the X-Ray diffraction results.

1. Introduction

Crystallization is a key unit operation of the pharmaceutical industry: over 90% of all pharmaceutical products contain drug substances in particulate form (Hacherl, et al., 2003). In the pharmaceutical industry, there is a significant need to control the particle size distribution and the purity of a drug substance typically via crystallization (Kirwan and Orella, 2002). In this study, griseofulvin, an active pharmaceutical ingredient (API) was chosen as a model material for experimentation in order to investigate the crystallization behavior of a Biopharmaceutics Classification System (BCS) Class IV drug, i.e., a drug that has poor solubility in water. The solubility of Class IV compounds greatly depends on the particle size, morphology, and size distribution. Thus, reducing the particle size of the drug compound increases the surface area per unit

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volume, which, in turn, improves the dissolution rate and bioavailability. Previous studies have looked at griseofulvin as a model drug for micronization. Several of these studies utilized a supercritical antisolvent precipitation process for crystallizing the griseofulvin and achieved long needle-like particles ranging from 2-50 μm (Chattopadhyay and Gupta, 2001), 40 μm-20 mm (De Gioannis, et al., 2004), to a few millimeters (Reverchon and Della Porta, 1999). However, no attention has been paid to the micronization of griseofulvin with an impinging jet mixer until now, which have been known to provide high yield throughputs of micron-sized particles with consistent reproducible results (Paul et al., 2004).

2. Experimental System and Methods

2.1 Materials

Griseofulvin ($C_{17}H_{17}ClO_6$), a highly hydrophobic compound (water solubility less than 0.2 mg/mL at 25°C (International Agency for Research on Cancer, 2001)), was kindly donated by Johnson & Johnson. Griseofulvin is slightly soluble in various organic solvents, including acetone, which was chosen as the solvent for this study (technical grade, purity: 99+%, Acros Organics, Somerville, New Jersey). Distilled water was chosen as the anti-solvent. Depending on the experiment, the anti-solvent solution was water added with a surfactant (Polysorbate 80, commercially known as Tween® 80) or a polymer/surfactant combination (hydroxypropyl methylcellulose (HPMC) and sodium dodecyl sulfate (SDS), respectively) to control particle size and particle agglomeration.

2.2 Experimental Apparatus

The design of the impinging jet mixer experimental apparatus was based upon the Bristol-Myers Squibb Company patent by Lindrud et. al. (2001). All components of the apparatus were purchased separately, and the apparatus was assembled and tested. The system consisted of an impinging jet device placed in a stirred tank and fed, through pumps, with the solvent and anti-solvent solutions stored in feed tanks. Figure 1 displays a schematic of the finalized experimental apparatus. All vessels were jacketed glass tanks. The two feed vessels were 1000 mL in volumetric capacity, while the main process vessel had a maximum capacity of 4000 mL, although, this larger capacity was never utilized during the experiments. Two centrifugal pumps (KL3404, Baldor Industrial Motor, Sonoma, California, for anti-solvent solution and VL3507, Baldor Industrial Motor, Sonoma, California, for drug solution) were used to pump the two solvents through the tubing at the desired flow rates. The flow rates were measured using two also identical rotameters (Gilmont® ccucal® Flowmeters, 65 mm scale). The majority of the tubing in the system was 0.25 inch (6.35 mm) stainless steel. The more flexible tubing was 0.375 in (9.525 mm) high-density polyethylene (HDPE), which was chemically and thermally compatible with the solvents at the operating temperature and pressure. The jet nozzles had 0.020 in (0.508 mm) internal diameters, and 0.0625 in (1.59 mm) outer diameters. They were held in place with a compression fitting stainless steel elbow with custom-made delrin collars. Two custom-made brackets secured the stainless steel tubing feeding the jets within the main process vessel. These brackets not only kept the tubing from moving during experiments, but also allowed for any adjustments between experiments. The distance between the jets, the angle of

impingement of the jets, and the location of the jets within the vessel could be easily adjusted. A sonicator probe (Omni Ruptor 250 Ultrasonic Homogenizer, Model #OR250-115, Omni International, Inc., Marietta, GA) placed within the main process vessel was additionally used in some experiments. This sonicator could operate at a maximum level of 250 W.

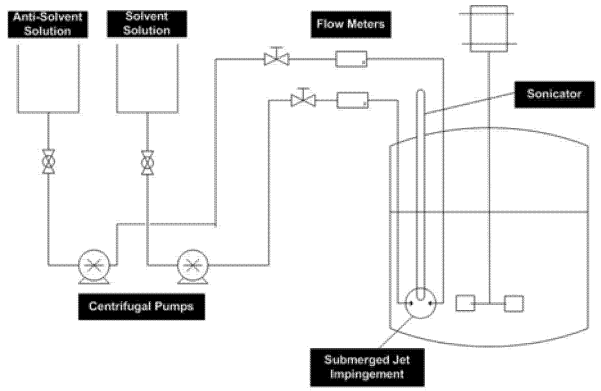

Figure 1. Schematic of experimental impinging jets apparatus.

2.3 Experimental Approach

The strategy of this experimental study was developed using a Design of Experiments (DOE) approach. The total number of possible input variables (or factors) was first established and for each of these factors, and the total number of desired treatments (or levels) was determined. Three factors were investigated in this study. These factors included the angle of impingement of the two jets, the presence of sonication, and the intensity of the sonication. The angle of impingement of the two jet streams was either 120^{o} or 180^{o}. When present, the concentration of Tween® 80 in the antisolvent solution was 0.0125 mM (0.015 mL/L), which is the critical micelle concentration in water (Balakrishnan, et al., 2004). Alternatively, the concentrations of HPMC and SDS, when utilized, in the final solution were both 0.075%W/V. Five separate sonication powers were studied: 0 W, in the case with no sonication, 75 W, 125 W, 200 W, and 250 W. The particle size distribution of the experimental samples was determined using laser diffraction particle size analysis. For this study, a Beckman-Coulter LS230 was utilized. Experimental samples were also analyzed using Scanning Electron Microscopy (SEM) and X-Ray Diffraction (XRD) to confirm the results of the Beckman-Coulter LS230 and determine crystal morphology. For this study, a LEO 1530 VP field-emission scanning electron microscope (FE-SEM) and Philips PW3040 X-Ray Diffractometer were utilized.

3. Results and Discussion

The DOE investigation involved understanding the effect of angle of impingement, presence of sonication, and the sonication power intensity. Two angles of impingement

between the two jet nozzles were investigated: 120°, and 180°. The two levels of sonication included no sonication (0 W) and the sonicator probe not being present during the experiment, and sonication power at 125 W and being delivered to the impingement point of the two jet streams with the sonicator probe. All experiments were conducted using the impinging jets apparatus shown in Figure 1. For each of these experiments, the solvent flow rate and jet velocity were kept constant at 32.3 mL/min and 2.66 m/s respectively. The temperatures of the solvent and antisolvent streams were maintained between 23-27 °C. For each experiment, the particle size distribution was determined multiple times with the Beckman-Coulter LS230 apparatus, and the results averaged accordingly.

Figure 2 summarizes the results of the griseofulvin mean particle size as a function of angle of impingement and the presence of sonication. These results are averages of replicate experiments run under similar experimental conditions. Figure 2 shows that the presence of sonication in a submerged impinging jets mixing system has a great impact on the mean particle size of the precipitated griseofulvin. For example, the mean particle size of griseofulvin dropped from 176.2 μm with no sonication to 38.23 μm in the presence of sonication (125 W), a reduction of 78.3%. This decrease in particle size was expected as more energy was delivered to the precipitation zone between the two jet nozzles. This could also be seen in the results related to the angle of impingement of the jet nozzles. The results of Figure 2 also show that the impinging jets system produced crystals with smaller mean particle sizes when the two jets were oriented 180º degrees apart and pointed directly at each other. For example, the mean particle size of griseofulvin dropped from 38.23 μm in the case with 125 W of sonication at an angle of impingement of 120° to 18.68 μm in the case with 125 W at an angle of impingement of 180°, a reduction of 51.1%. Having the two jet streams colliding with the jet nozzles oriented at 180º apart maximizes the kinetic energy of the streams, while minimizing the mixing time of the streams. Though this increase in kinetic energy between the 120º

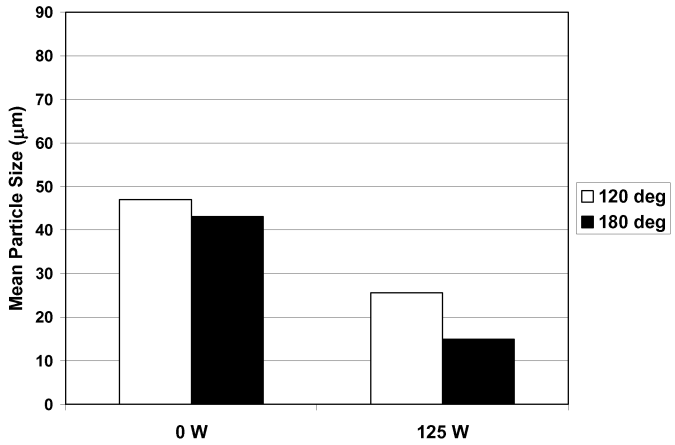

Figure 2. Mean particle size (μm) of griseofulvin as a function of angle of impingement and sonication presence.

angle of impingement and 180º angle of impingement is small in comparison to the energy provided by the sonicator, it is still significant enough to show a difference in all experimental cases. The sonication power intensity factor included five levels. These five levels were the following sonication power intensities: 0 W (no sonication), 75 W, 125 W, 200 W, and 250 W. All experiments were conducted using the impinging jets apparatus shown in Figure 1. A temperature difference between the two jet streams of 28°C, the angle of impingement of 180°, an anti-solvent solution of distilled water and a combination of HPMC and SDS, and the solvent flow rate and jet velocity were kept constant at 32.3 mL/min and 2.66 m/s respectively for these experiments. For each experiment, the particle size distribution was determined multiple times with the Beckman-Coulter LS230 apparatus, and the results averaged accordingly. Figure 3 summarizes the results of the griseofulvin mean particle size as a function of the sonication power. These results are averages of replicate experiments run under similar experimental conditions. The combination of HPMC and SDS helped to stabilize the griseofulvin in the mostly water-based suspension. The mean particle sizes at sonication powers equal to, or larger than, 200 W did not change appreciably with sonication power, and was only slightly smaller than the size obtained at 125 W. Thus, it was determined that a sonication power intensity of 125 W or greater and an antisolvent solution containing a mixture of HPMC and SDS should be utilized.

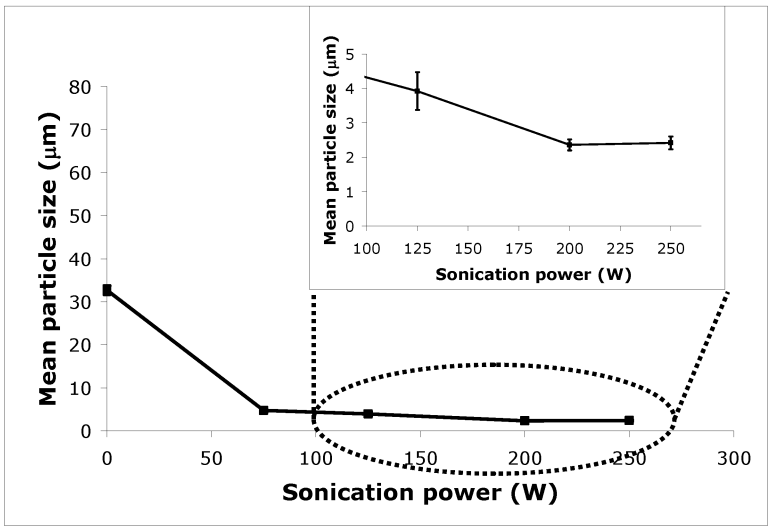

Figure 3. Mean particle size (μm) of griseofulvin as a function of sonication power.

4. Conclusion

The precipitation of griseofulvin micro/nanoparticles was achieved by the antisolvent crystallization method using the impinging jets mixer. This investigation has shown that the impinging jets system produced crystals with smaller mean particle sizes when the two jets were oriented 180° apart and pointed directly at each other than when the

two jets were oriented in a 120^{o} configuration. Also, the introduction of ultrasonic power at the impingement point resulted in markedly smaller mean particle size and a tighter particle size distribution. Thus, it was determined that an angle of impingement of 180^{o} and the presence of sonication were important towards the rapid precipitation of griseofulvin. As the sonication power intensity was increased, the mean particle size decreased until an asymptotic value was reached. This asymptotic value was achieved at sonication powers above 125 W. Thus, it was determined that for optimum results a sonication power intensity of 125 W or greater and an antisolvent solution containing a mixture of HPMC and SDS should be utilized.

Acknowledgements

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