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ABSTRACT

PRECIPITATION OF MICRO/NANOPARTICLES IN ENHANCED HIGH ENERGY DISSIPATION MIXING SYSTEMS

by Giuseppe Di Benedetto

Crystallization is the most common unit operation used in the pharmaceutical industry to synthesize active ingredients. Rapid development of a drug candidate is dependent on the ability to produce a desired drug substance with consistent properties. These properties include stability and purity, which are directly affected by the crystallization process and which affect, in turn, bioavailability, drug dissolution rate, drug stability, and shelf life.

The objective of this work is to produce micro/nanoparticle crystals within existent glass-lined pharmaceutical stirred-tank reactors by modifying the current reactor configuration to include features that can increase the local rate of energy dissipation in the mixing precipitation zone where crystals are formed, thus promoting the formation of micro/nanoparticles. In this work, a submerged impinging jet system placed inside the tank was used in combination with another energy dissipation device, i.e., a sonicator, to achieve this objective. The hydrodynamics of the typical reactor used in the pharmaceutical industry for this purpose, namely a partially baffled cylindrical reactor stirred by a retreat-blade impeller, was first predicted using Computational Fluid Dynamics (CFD). Laser Doppler Velocimetry (LDV) was used to validate the CFD predictions of the velocity distribution in the reactor and especially in the mixingprecipitation zone. Then, the performance of the system was evaluated using an actual precipitation reaction of relevance to the pharmaceutical industry, namely the an aqueous solution as the antisolvent. Precipitation studies were conducted to determine the role on crystal size distribution of different operating parameters, such as impinging jet velocity, angle of impingement, sonication power, and the presence of different surfactants. Several characterization techniques such as Scanning Electron Microscopy (SEM), Laser Diffraction Particle Size Analysis, and X-Ray Diffraction (XRD) were utilized to determine the particle size distribution, particle shape, and crystal morphology.

The submerged impinging jets system produced crystals with smaller mean particle sizes 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. In general, the results were highly reproducible. X-Ray diffraction results showed that the crystal structure was unaffected by different operating conditions.

A similar investigation was conducted on a new type of confined impinging jets system. This newly fabricated system allowed for the introduction of ultrasonics within a small, confined impinging jets chamber. The key parameters investigated in this study were the antisolvent-to-solvent mass flow ratio and the sonication power intensity. The mass flow ratio between the antisolvent stream and the solvent stream had a major effect on the resulting mean particle size and accompanying particle size distribution. The higher mass flow ratios delivered a faster precipitation process resulting in smaller mean particle size and tighter particle size distribution. The addition of sonication to the confined impinging jets apparatus resulted in a significant reduction in the mean particle size which was between $1-2 \mu m$.

PRECIPITATION OF MICRO/NANOPARTICLES IN ENHANCED HIGH ENERGY DISSIPATION MIXING SYSTEMS

by Giuseppe Di Benedetto

A Dissertation Submitted to the Faculty of New Jersey Institute of Technology in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Chemical Engineering

Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering

January 2009

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APPROVAL PAGE

PRECIPITATION OF MICRO/NANOPARTICLES IN ENHANCED HIGH ENERGY DISSIPATION MIXING SYSTEMS

Giuseppe Di Benedetto

Dr. Piero M. Armenante, Dissertation Advisor Distinguished Professor of Chemical Engineering, NJIT	Date
Dr. Robert Barat, Committee Member Professor of Chemical Engineering, NJIT	Date
Dr. Rajesh N. Davé, Committee Member Distinguished Professor of Chemical Engineering, NJIT	Date
Dr. Somenath Mitra, Committee Member Professor of Chemistry and Environmental Science, NJIT	Date

Dr. Paul Takhistov, Committee Member Associate Professor of Food Engineering, Department of Food Science Rutgers University, New Brunswick, NJ

Date

BIOGRAPHICAL SKETCH

Author: Giuseppe Di Benedetto

Degree: Doctor of Philosophy

Date: January 2009

Undergraduate and Graduate Education:

- Doctor of Philosophy in Chemical Engineering, New Jersey Institute of Technology, Newark, NJ, 2009
- Bachelor of Science in Chemical Engineering, New Jersey Institute of Technology, Newark, NJ, 2002

Major: Chemical Engineering

Presentations and Publications:

Giuseppe Di Benedetto (presenter), Ankit Patel, Ewa Sukcik, Piero M. Armenante, and Somenath Mitra,
"Effect of Operating Conditions on the Precipitation of Griseofulvin in Impinging Jets in Stirred-Tank Reactors," AIChE Annual Meeting, Philadelphia, PA, November 16-21, 2008.

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Retreat-Blade Impeller,"
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 Giuseppe Di Benedetto (presenter), Ewa Sukcik, Piero Armenante, and Somenath Mitra,
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Giuseppe Di Benedetto (presenter) and Piero Armenante,

"Experimental and Computational Determination of the Hydrodynamics in a Stirred Tank Reactor Provided with a Retreat Blade Impeller," AIChE Annual Meeting, San Francisco, CA, November 12-17, 2006.

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"Computational and Experimental Determination of the Velocity Distribution in a Stirred Reactor with a Retreat Blade Impeller Using LDV Experimentation and CFD Modeling,"

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NOMENCLATURE

Chapter 2

$C_{1arepsilon},C_{2arepsilon},C_{3arepsilon}$	Empirical constants
C_{μ}	Constant, except in realizable k-e turbulence model
g	Gravitational acceleration (m/s ²), standard value = 9.80665 m/s^2
G_b	Generation of turbulence kinetic energy due to buoyancy
G_k	Generation of turbulence kinetic energy due to the mean velocity gradients
G_ω	Generation of turbulence kinetic energy due to specific dissipation rate
k	Kinetic energy per unit mass (J/kg)
Р	Pressure (Pa)
$S_k, S_{\varepsilon}, S_{\omega}$	User-defined source terms
U	Fluid velocity magnitude(m/s)
\overline{u}	Mean fluid velocity (m/s)
<i>u'</i>	Fluctuating fluid velocity (m/s)
Y_k	Dissipation of k due to turbulence
Y_M	Contribution of fluctuating dilation in compressible turbulence to the overall dissipation rate
Y_{ω}	Dissipation of ω due to turbulence
$lpha_k$	Inverse effective Prandtl number for k

NOMENCLATURE (Continued)

Chapter 2 (continued)

$lpha_arepsilon$	Inverse effective Prandtl number for ε
Е	Turbulent dissipation rate (m^2/s^3)
μ	Dynamic viscosity (cP)
μ_{eff}	Effective viscosity (cP)
μ_t	Turbulent viscosity (cP)
ν	Kinematic viscosity (m ² /s)
ρ	Density (kg/m ³)
σ_k	Turbulent Prandtl number for k
$\sigma_{arepsilon}$	Turbulent Prandtl number for ε
ω	Specific dissipation rate (s ⁻¹)
Γ_k	Effective diffusivity of k
Γ_{ω}	Effective diffusivity of ω

NOMENCLATURE (Continued)

Chapters 3 and 4

Y_{ijk}	Measured variable
μ	Common effect in all observations
$\mathcal{E}_{k(ij)}$	Error within each of the treatment combinations
Р	Sonication power treatment
S	Surfactant choice treatment
R	Drug-to-HPMC-to-SDS mass ratio treatment
М	Antisolvent-to-Solvent mass flow ratio treatment

CHAPTER 1 INTRODUCTION

1.1 Mixing in the Pharmaceutical Industry

In the pharmaceutical and specialty chemical industries, a large majority of the mixing and reaction/precipitation operations are conducted in the batch or semibatch mode [1]. In most cases such operations are carried out in multi-purpose, non-dedicated stirred vessel, which offer the distinct advantage of being flexible and readily adaptable to different types of reactions conducted in them [1]. Stirred tank reactors have some other distinct advantages which make them the type of reactor chosen for pharmaceutical and chemical processes [2]. In most chemical reactions of industrial relevance, a complete conversion of the limiting reagent is generally desired [2]. The progression toward completeness of the conversion can be easily monitored over time when stirred tank reactors are operated in batch or semibatch mode [2]. This may not necessarily be the case for a continuous stirred tank reactor, which controls conversion completeness with residence time distribution [1]. The reagent or additive quantities can also be carefully controlled using stirred tank reactors [1]. This allows for increased accuracy in operating the process [1]. The volume of stirred tank reactor can be easily controlled and varied as required by the process [3]. Stirred tanks are also very versatile as reactors since they can process a large variety of processes with little modification of the internals and can be used in dedicated or multipurpose facilities [2].

The stirred tank reactor does have its disadvantages that could affect a given process [2]. Though their large volumes can be an advantage, it could also be a significant disadvantage [2]. The mixing intensity throughout the vessel is nonuniform

and can cause variations in local concentration environments [2]. This can in turn lead to poor results either because of the non-homogeneity of the mixture or because of undesirable side reactions [2]. Another significant disadvantage stems from the optimum operating conditions of a given process [1]. Though these reactors are easily modified for alternative processes, these modifications cannot be made during mid-operation [1]. So in the case where a process requires different optimum conditions for separate portions of the process, the operating conditions might not necessarily match the optimum conditions [1]. An example of such a problem would be in the case of a reaction that results in the precipitation of a product, but the reaction and precipitation steps might require different mixing intensities [1]. Disadvantages such as these has made the fluid dynamic study of mixing in these reactors imperative for increasing the success rate of conducting processes within them [1].

The stirred tank reactor vessels (pictured in Figure 1.1) used in the pharmaceutical and fine chemical industries are typically constructed with glass-lined walls and internal equipment, including the impeller and baffle, in order to prevent contamination of the products and reduce the occurrence of corrosion. Historically, this has significantly limited the ability of equipment manufacturers to fabricate systems with full baffling and optimal impeller configuration [3]. The retreat-blade and anchor impellers have been used for years in these glass-lined vessels due to their ease of manufacturing [3]. However, recent advances in manufacturing methods have allowed for the development of glass-lined impellers with more sharply angled shapes [4]. Today, glass-lined versions of pitched-blade, hydrofoils, and other impellers are manufactured for use in the pharmaceutical and fine chemical industries [4].

Nevertheless, glass-lined, retreat-blade impeller systems remain the most common type of reactor configuration used [4].



Figure 1.1 Typical baffle arrangement in a glass-lined tank.

Glass-lining has also limited the design and effectiveness of baffles over the years [1]. Fortunately, glass-lined baffles have also experienced a design renaissance in recent years [1]. Their development has resulted in the enhancement in mixing performance in these systems [1]. However, the number of baffles used in glass-lined vessels has always been limited [2]. Typically, only a single baffle is used in order to maximize the number of nozzles available in the vessel lid for other purposes [2]. Being only partially baffled can seriously affect the mixing performance of the system, regardless of the advancements in the design [2]. Although partially baffled, retreat blade impeller systems are critical in pharmaceutical production. There is little information available to date on their hydrodynamics [3, 4, 5, 6, 7, 8, 9]. With a basic fluid dynamic knowledge of these systems, there will be a better understanding of the operation of vital processes,

such as solid suspension, crystallization and chemical reaction, regularly conducted within them [1].

1.2 Role of Crystallization in the Pharmaceutical Industry

Crystallization is a key unit operation of the pharmaceutical industry [10]. Over 90% of all pharmaceutical products contain drug substances in particle form [11]. Pharmaceutical companies invest a considerable amount of monetary resources for identifying and developing a suitable solid form of the drug substance [10]. Generally, these substances are produced in a crystalline form [11]. Rapid development of a drug candidate is dependent on the ability to produce a desired drug substance with consistent properties as early as possible [10]. These properties include stability and purity, which are directly affected by crystallization [10]. Improvements in stability and purity result in improvements in bioavailability, higher dissolution, decreased decomposition rate, and longer shelf-life [10]. All of these parameters must be considered during the design and development of a drug form [11].

In the pharmaceutical industry, there is a significant need to control the particle size distribution and the purification of a drug substance [10]. This is accomplished through the control of crystallization [10]. Unfortunately, the pharmaceutical industry works with new drug substances that are made up of complex organic compounds [10]. These chemical compounds are typically hydrophobic [10]. The chemical complexity of these entities creates difficulties for crystallization [10]. The solutions to these difficulties are sought through the various equipment and techniques used to perform crystallization in the pharmaceutical industry [10].

1.2.1 Introduction to Crystallization

Crystallization is a separation and purification technique utilized in the production of many different materials, and it is achieved via a phase change in which a crystalline product is obtained from a solution consisting of a mixture of two or more species in the form of a homogenous single phase [12]. Typically, this solution will contain a solute dissolved in a liquid solvent [12]. Crystallization will occur when the concentration of the solute exceeds its solubility within the solution [13]. This excess represents the driving force for crystallization called supersaturation [13].

Crystallization consists of two main steps: nucleation and crystal growth [13]. Nucleation, the phase separation when formation of new crystals takes place occurs when the solute molecules start to precipitate and gather into clusters, which become stable and begin to collect into crystalline form [14]. However when the clusters are not stable, they redissolve into the solution [14]. Therefore, in order for the clusters to remain in crystalline form, they need to reach a critical size [14]. This critical size is dictated by the operating conditions, such as temperature, supersaturation, etc. [14]. The stage of nucleation helps to establish the crystal structure of the precipitating particles [14]. There exist two main types of nucleation: primary and secondary [14]. Primary nucleation includes two sub-types: homogeneous nucleation and heterogeneous nucleation [14]. Homogeneous nucleation occurs spontaneously and randomly, but it is driven by superheating or supercooling of the medium [15]. Heterogeneous nucleation is induced by foreign particles and it is easier to understand and predict [15]. Instead, it is induced by

crystals of the same solute species [15]. These crystals might be present as a result of primary nucleation or seeding [15].

After the clusters have formed into stabilized crystals larger than the critical size, the second step of crystallization, crystal growth, commences [15]. Nucleation and growth continue to occur simultaneously for as long as the supersaturation exists [14]. Depending upon the operating conditions, either nucleation or growth may be predominant over the other [14]. As a result, crystals with various different sizes and shapes are produced [14]. The control of crystal size and shape is among the most important challenges in pharmaceutical development [11]. The crystallization is complete once the supersaturation is exhausted and the solid-liquid system reaches equilibrium [11].

1.2.1.1 Antisolvent Crystallization

The most common crystallization technique in the pharmaceutical industry is the solvent/antisolvent crystallization [15]. This technique works by first dissolving a solute in a solvent to create a homogeneous solution [15]. Then, the solution is forced into supersaturation by the addition of a substance that reduces the solubility of the solute in the solvent [15]. This substance may be a liquid, solid, or gas, but is typically a liquid when used in the pharmaceutical industry [15]. It is known as the "precipitant" or "antisolvent" and the solute is insoluble within it at the operating conditions [15]. For a liquid anti-solvent, the substance is required to be miscible with the solvent of the original solution [15]. This would result in a two phase solid-liquid system as opposed to a three phase solid-liquid-liquid system [15].
This technique is actually known by a variety of terms [15]. It can be referred to as "watering-out" crystallization in the pharmaceutical industry [15]. This term has been coined as a result of all the pharmaceutical drug substances that are insoluble in water [15]. Due to the chemical complexity of these drug substances, they are only soluble in organic solvents and water is utilized as the anti-solvent [15]. Hence, the drug substance is "watered-out" of the solution [15].

"Watering-out" has many advantages [15]. Highly concentrated initial solutions can be prepared by dissolving an impure crystalline material in a suitable solvent at suitable operating conditions [15]. If the solute is very soluble in the solvent, then a high solute recovery yield can be obtained by using a suitable anti-solvent in the process [15]. This typically results in better purification than is found from straightforward crystallization operation [15].

1.2.1.2 Reactive Crystallization

The other common crystallization technique used in the pharmaceutical industry is reactive crystallization [15]. A solid crystalline product is produced as a result of a chemical reaction typically between solutes initially dissolved in liquids rapidly mixed together to generate high local level of supersaturation [15].

1.3 Impinging Jet Mixer

A commonly used crystallizer in the pharmaceutical industry is the impinging jet mixer [10]. Impinging jet mixers consist of two jet nozzles arranged diametrically opposed to each other [16]. The outlet tips of the nozzles are directed to face each other [16]. The two fluids are then pumped through the nozzles at a high linear velocity until they meet



Figure 1.2 Impinging Jets [18].

There are two keys to proper, efficient rapid mixing [17]. The first is to produce a region of high turbulent energy dissipation, such as the impingement zone in impinging jet mixers [17]. The second is to ensure that the process streams pass through this high intensity region without bypassing [17]. The first criterion ensures the proper scale of mixedness for the process, while the second guarantees that the desired molar flow ratios of the feed streams are kept intact throughout the rapid mixing process [17].

The rapid mixing effect of impinging jet mixers makes them extremely useful crystallizers for production of micron-sized and nano-sized particles [16]. In order to produce such small sized particles using crystallization, the nucleation step must be enhanced while limiting the crystal growth step [10]. Rapid precipitation under high supersaturation conditions favors the former, and the combination of the impinging jet mixer's rapid mixing with the proper process streams will result in the desired small sized crystals [10]. Schaer et al. have shown that impinging jet mixers achieve extremely small mixing times [17]. When the mixing time is much smaller than the precipitation time, then the final product characteristics depend on physico-chemical parameters and not on mixing conditions [17]. When the mixing time is comparable to, or larger than, the precipitation time, the properties of the final product are greatly affected by mixing [17].

There are two different types of impinging jet mixers: submerged and confined [16]. Both types of impinging jet mixers were originally used in industrial applications by Midler, Jr. et al. in 1994 under the assignee of Merck & Company, Inc [16]. Then, Lindrud et al. improved upon the Midler, Jr. et al. design of the submerged impinging jet mixer in 2001 under the assignee of Bristol-Myers Squibb Company [19].

1.3.1 Submerged Impinging Jet Mixer

In a submerged impinging jet mixer, the two jets nozzles for the feed streams are submerged within a large stirred tank or chamber [16]. The jets are oriented in a similar manner as described above [16]. The walls of the tank or chamber have little effect on the impingement process of the mixer [17]. The tank or chamber can be filled with a gas or fluid to aid in the crystallization process [17]. For example, in an anti-solvent crystallization process, the tank might be filled with a small volume of water acting as an anti-solvent [17].

Some researchers have split up submerged impinging jet mixers into further classifications [17]. They refer to an impinging jet mixer that is submerged in a low viscosity fluid as a "free impinging jet mixer" [17]. Then, they consider an impinging jet mixer submerged in a higher viscosity fluid to be a "submerged impinging jet mixer" [17]. Unfortunately, these classifications appear to not have caught on as the majority of researchers consider all of them to be simply "submerged impinging jet mixers" [17].



Figure 1.3 Schematic of submerged impinging jet mixer [16].

Midler, Jr. et al. performed anti-solvent crystallization studies within a submerged impinging jet mixer [16]. One such study was the crystallization of simvastatin (Zocor®) using methanol as the solvent [16]. Simvastatin was dissolved in methanol at 55°C, and water was used as the anti-solvent [16]. The water anti-solvent was heated to 85° C, and the vessel was partially filled with a seeded anti-solvent [16]. The two jet flow rates were 1.1 L/min, with 23 m/s as the corresponding linear velocities [16]. This particular study resulted in particles with a surface area of $3.1\pm0.4 \text{ m}^2/\text{g}$ [16]. All of the studies by Midler, Jr. et al. for submerged impinging jet mixers resulted in particles within the size range of 3-20 microns [16].



Figure 1.4 Schematic of submerged impinging jet with sonication [19].

In 2001, Lindrud et al. improved upon the design of the submerged impinging jet mixer of Midler, Jr. et al. [19]. The invention of Midler, Jr. et al. only utilized the submerged impinging jet mixer alone [16]. Lindrud et al. combined the submerged impinging jet mixer with ultrasonics in the form of a sonication probe [19]. The sonication probe was located in the zone of impingement, and was used at maximum power throughout this study [19].



Figure 1.5 Close-up schematic of sonicator probe within impingement zone [19].

Lindrud et al. also worked with examples utilizing anti-solvent crystallization [19]. One study was the anti-solvent crystallization of (Z-3-[1-(4-chorophenyl)-1-(4-methylsulfonylpenyl) methylene]-dihydrofuran-2-one dissolved in dimethyl sulfoxide (DMSO) at 65° C- 75° C [19]. The anti-solvent for this case was water chilled to 2° C, and a small portion was charged to the tank vessel before the process start-up [19]. Once process commenced, the solvent solution jet flow rate was 0.18 kg/min and the anti-solvent jet flow rate was 0.72 kg/min, which is a 4:1 molar ratio [19]. Both jets had a linear velocity of 12 m/s [19]. The resulting crystal product from these studies had a mean particle size of 500 nm, as can be seen in Table **1.1** [19].

Mean Crystal Size (μm)	% <0.5 <i>μ</i> m	95th percentile (μm)
0.5090	99.011	0.5086
0.5124	98.097	0.5087
0.5376	92.224	0.9373
0.5164	97.499	0.5087
0.5178	97.093	0.5088
0.5129	97.987	0.5087

 Table 1.1 Summary of experimental results of Lindrud et al. [19].

The smaller particles sizes achieved by Lindrud et al. were a result of the incorporation of ultrasonics in the apparatus [19]. This phenomenon has an analog in the dispersion of immiscible liquids. As seen in Figure 1.6 below, the sizes of droplets of a liquid dispersed in another immiscible liquid decreases as the energy dissipated in the system increases [20]. Impinging jets alone have energy dissipation rates at 10^5 W/kg, which results in a corresponding particle size of around 10 microns [20]. However, ultrasonics have energy dissipation rates at around 10^5 W/kg, which results in a corresponding to particle size of around 10 microns [20]. However, ultrasonics have energy dissipation rates at around 10^5 W/kg, which results in a corresponding droplet size of 500 nm [20]. Thus, the benefit of sonication is obvious [20].



Figure 1.6 Particle size as a function of energy dissipation [20].

Another submerged impinging jet mixer projects worth noting comes from Am Ende et al [21]. They studied and patented reactive crystallization within the Midler, Jr. et al. apparatus for submerged impinging jet mixers [21]. In one case, they performed reactive crystallization of 5,8,14-triazatetracyclo[10.3.1.02,11.04,9]-hexadeca-2-(11),3,5,7,9-pentaene [21]. This reactant was dissolved in an ethyl acetate solution, and the other reactant (L)-tartaric acid was dissolved in a methanol solution [21]. Both solutions were prepared and kept at room temperature [21]. The solution within the stirred tank was seeded with 20 mg of 5,8,14-triazatetracyclo[10.3.1.02,11.04,9]-hexadeca-2-(11),3,5,7,9-pentaene (L)-tartrate and equal parts methanol and ethyl acetate [21]. The flow rate for both jets was 20 mL/min, with a 13.4 m/s linear velocity [21]. The resulting mean particle size was 10 microns, with 5% of particles less than 5 microns and 95% of particles less than 15 microns [21].

1.3.2 Confined Impinging Jet Mixer

In a confined impinging jet mixer, the two jets nozzles for the feed streams are connected to a small chamber [16]. The jets are oriented in a similar manner as described above for the general description of an impinging jet mixer [16]. The walls of the chamber have a large effect on the impingement process of the mixer as it "confines" the mixing volume [17]. The chamber can be filled with a gas or fluid to aid in the crystallization process, but it usually remains empty [17]. The resulting product discharges into a large vessel and continues on with the various post-crystallization processes [17].



Figure 1.7 Schematic of confined impinging jet mixer [16].

Midler, Jr. et al. also conducted studies for this other invention in a similar fashion to the submerged impinging jet mixer studies [16]. They performed anti-solvent crystallization studies within a confined impinging jet mixer [16]. One such study was the crystallization of omeprazole (Prilosec®) using methanol as the solvent [16]. Omeprazole was dissolved in methanol at 42°C, and water with the surfactant Triton X-100 was used as the anti-solvent [16]. The water anti-solvent was heated to 42°C [16]. The two jet flow rates were 0.7 L/min, with 15 m/s as the corresponding linear velocities [16]. This particular study resulted in cube-like particles with 95% of them smaller than 3 microns [16].



Figure 1.8 Schematic of confined impinging jet mixer with discharge into generic receiving vessel [16].

Similarly, Am Ende et al also studied confined impinging jet mixers [21]. They studied and patented reactive crystallization within the Midler, Jr. et al. apparatus for confined impinging jet mixers [19]. In one case, they performed reactive crystallization of ziprasodone [21]. This reactant was dissolved in an tetrahydrofuran (THF) solution, and the other reactant was an aqueous hydrochloric acid solution [21]. The THF solution was prepared and maintained at 60°C, while the HCl solution was maintained at 15°C [21]. The flow rate for the THF solution jet was 120 mL/min, with a 9.9 m/s linear velocity [21]. The flow rate for the HCl solution jet was 22.5 microns, with 0% of particles less than 1 micron and 90% of particles less than 41 microns [21].

Other researchers have been more successful with achieving smaller particle sizes using the confined impinging jet mixer [22]. Marchisio et al. used reactive crystallization of solid barium sulfate to test the ability of the system to produce consistent results [22]. The two reactant solutions for this study were barium chloride and sodium sulfate [22]. Marchisio et al. performed experiments with six different molar ratios between the two reactants [22]. Their results show that attention should always be devoted to the chemical "recipe" suitable for obtaining a specific product [22]. Smaller particle sizes are obtained if the molar feed ratio is optimized [22]. Nevertheless, the interplay between mixing and precipitation is crucial [22]. By only changing the mixing conditions and keeping the same chemical "recipe," the mean particle size was reduced from a few microns down to 80 nm [22].

Other researchers have been more successful with achieving smaller particle sizes using the confined impinging jet mixer [22, 23]. Marchisio et al. used reactive crystallization of solid barium sulfate to test the ability of the system to produce consistent results [22]. The two reactant solutions for this study were barium chloride and sodium sulfate [22]. Marchisio et al. performed experiments with six different molar ratios between the two reactants [22]. Their results show that attention should always be devoted to the chemical "recipe" suitable for obtaining a specific product [22]. Smaller particle sizes are obtained if the molar feed ratio is optimized [22]. Nevertheless, the interplay between mixing and precipitation is crucial [22]. By only changing the mixing conditions and keeping the same chemical "recipe," the mean particle size was reduced from a few microns down to 80 nm [22]. Johnson and Prud'homme used anti-solvent crystallization of a hydrophobic drug compound [23]. They dissolved an amphiphilic diblock copolymer, the drug compound, and any other hydrophobic component in a water-miscible solvent such as a tetrahydrofuran (THF) [23]. Then, they fed the solution in a stream through the confined impinging jet mixer chamber, where it collided at equal

momentum with an opposing water stream [23]. This would lead to the formation of nanoparticles [23]. Specifically, Johnson and Prud'homme produced β -carotene loaded polyethylene oxide-b-polystyrene (1,000 g/mol) block copolymer nanoparticles with an average diameter of 88 nm [23].

1.4 Objectives of this Work

The above review shows that there is significant room for improvement in reactive precipitation processes in the pharmaceutical industry. On the one hand, our current understanding of the hydrodynamics of partially-baffled, glass-lined, stirred tank reactors limits our ability to use them effectively when rapid precipitations is conducted in them. On the other hand, stirred-tank reactors have intrinsic limitations due to their spatial and temporal non-homogeneity, requiring the use of improved, continuous reactor designs, such as high-energy impinging jets systems, to be overcome.

This work initially focused on the first of these two tasks and resulted in ongoing work aimed a fully characterizing glass-lined system. As the project matured, the emphasis shifted to the study of jet mixers for pharmaceutical operations to be used either on their own or in combination with glass-lined vessels. Therefore, both aspects are reflected in the work carried out. A list of the objectives for this project is the following:

- Characterize the flow field developed in glass-lined stirred-tank reactors using both an experimental approach based on Laser-Doppler Velocimetry (LDV) and a computational approach based on Computational Fluid Dynamics (CFD)
- Investigate the effect on the flow field in glass-lined tank reactors of:
 - o no baffling versus partial baffling configuration

- shape of vessel bottom
- Produce micro/nanoparticle crystals of an API within glass-lined stirred-tank reactors by use of impinging jets
- Assess the impact of different process intensification/enhancement techniques on impinging jet precipitation including:
 - o submerged versus non-submerged configuration
 - o sonication
 - o surfactant addition
- Determine the effect on particle size distribution and crystal morphology of operating variables such as:
 - o jet velocity
 - angle of impingement
 - surfactant/polymer type and concentration
 - o sonication power
 - difference in temperature of streams
- Investigate the use of a Confined Impinging Jets Mixer with the same solvent/antisolvent system used for the Submerged Impinging Jets study.

CHAPTER 2

COMPUTATIONAL AND EXPERIMENTAL INVESTIGATION OF THE HYDRODYNAMICS IN A STIRRED REACTOR WITH A RETREAT BLADE IMPELLER

2.1 Background

Since one of the main goals of the project is to understand the fluid dynamics of a typical glass-lined stirred tank reactor system used in the pharmaceutical industry, the laboratory experimental apparatus must reflect the same flow phenomena found in the industrial sized apparatus. Two major companies manufacture glass-lined stirred tank reactors for pharmaceutical companies, i.e., Pfaudler, Inc. and De Dietrich. Both companies were contacted for dimensional information regarding their industrial glass-lined equipment. Eric Momsen, Process engineer, for De Dietrich's Union, NJ, kindly provided schematics and dimensions for their 5, 10, 50, and 100 gallon reactor systems [24]. The 100 gallon (378.5 L) reactor system (shown in Figure 2.1) is De Dietrich's most commonly sold apparatus for pharmaceutical applications [24]. Thus, it was chosen as the model for the scaled-down laboratory experimental apparatus used in this work.

Using the De Dietrich 100 gallon (378.5 L) reactor system as a model, the dimensions for a laboratory-scaled retreat blade impeller and BeaverTail baffle were drawn up. The dimensions for both the impeller and baffle were based upon the geometric ratios from the industrial sized system and assumed the use of glass vessels with a diameter, T, of 8.44 in (300 mm). The comparison of the dimensions of the industrial reactor and the dimensions of the laboratory-scale vessels used in this work are summarized in Table **2.1**.



Figure 2.1 De Dietrich 100 gallon reactor system [25].

John Korzun and Dr. San Kiang of Bristol-Myers Squibb Company in Piscataway, NJ, played an extensive role in the construction of the impeller and baffle. The aluminum laboratory-scaled retreat blade impeller and Beavertail baffle mentioned below were constructed by a machine shop recommended by them.

2.2 Experimental Materials, Equipment and Methods

2.2.1 Materials

Distilled water was the liquid used in all the fluid dynamic experiments and simulations conducted in this component of the work. The stirred tank reactor was filled with distilled water up to the desired level, which was always equal to the diameter of the vessel (Table **2.1**).

Silver-coated hollow glass spheres purchased from Dantec Dynamics (Dantec Measurement Technology USA, Mahwah, NJ, USA) were used as the seed particles for

LDV experiments. These particles had a 10- μ m mean particle size, a particle size distribution range of 2-20 μ m, and a density of 1.4 g/cm³. The seed particles were used to follow the flow of the fluid and scatter the laser light used by the LDV system to measure the fluid velocity.

Table 2.1 Dimensions of the industrial reactor (De Dietrich) and the laboratory-scale equipment (flat-bottom and hemispherical-bottom tanks).

Tank Dimensions	De Dietrich		Flat-Bottom		ChemGlass Hemispherical Bottom	
	gal	L	gal	L	gal	L
Volume, V	100.0	378.5	4.906	18.57	4.227	16.00
	inches	mm	inches	mm	inches	mm
Tank Diameter, T	32.00	812.8	11.30	287.0	11.81	300.0
Liquid Height, H	32.00	812.8	11.30	287.0	11.81	300.0
Retreat Blade Impeller Dimensions					· ·	<u>. </u>
Diameter, D	24.00	609.6	8.625	219.1	8 625	219.1
Impeller Bottom Clearance, Cb	2.875	73.03	1.061	26.95	1.061	26.95
Blade Cross-Section						
height, h	2.362	60.00	1.000	25.40	1.000	25.40
width, w	1.339	34.00	0.500	12.70	0.500	12.70
Blade Radius of Curvature, r	10.00	254.0	3.625	92.08	3.625	92.08
						: • • • • • • • • • • • • • • • • • • •
Beaver-Lail Baffle Dimensions					·	
Baffle Clearance, C _{baffle}	11.00	279.4	3.553	90.23	3.553	90.23
Baffle Wall Clearance, δ _b	4.400	111.8	1.166	29.60	1.245	31.64
Top Section			-			
Diameter	3.000	76.2	0.600	15.24	0.600	15.24
Length	19.06	484	2.781	70.64	2.781	70.64
Middle Section						
Diameter	4.646	118.0	0.875	22.23	0.875	22.23
Length	16.00	406.0	7.862	199.7	7.862	199.7
Bottom Section						1
Diameter	4.016	102.0	0.790	20.07	0.790	20.07
Length	7.000	178.0	2.781	70.64	2.781	70.64

2.2.2 Experimental Apparatus

The retreat blade impeller (D = 8.625 in = 219.1 mm) used here was manufactured specifically for this study and had three identical blades with a 3.625 in (92.08 mm) radius of curvature, and a central hub to fit a 0.5 inch (12.7 mm) shaft. The blades were located 120° apart on the hub, similar to the industrial model. The Beavertail baffle contained three separate major sections: the 2.781 in (70.64 mm) length top section, the flattened 7.862 in (199.7 mm) length middle section, and the 2.781 in (70.64 mm) bottom section. The flattened area covered 7.395 square inches (4770 square mm). Figure 2.2 displays the laboratory-scale retreat blade impeller and Beavertail baffle used in this study.



Figure 2.2 Laboratory-scale retreat blade (left) and BeaverTail baffle (right) used in this study.

Two separate tank configurations were investigated in this study. The first was a flat-bottomed glass tank with a diameter, T, of 11.30 in (287 mm), and a liquid height of 11.30 in (287 mm). The second configuration was a ChemGlass tank with a hemispherical bottom (ChemGlass #CG-1968-61) having a diameter, T, of 11.81 in (300 mm), and a liquid height of 11.81 in (300 mm). All ChemGlass equipment was kindly

donated by ChemGlass President/CEO Steve Ware. Figure 2.3 displays both the flatbottom tank and ChemGlass hemispherical bottom tank.



Figure 2.3 Flat-Bottom vessel (left) and ChemGlass hemispherical bottom vessel (right) used in this study.

Two separate configurations were investigated for each vessel. The first involved the use of the retreat blade impeller and Beavertail baffle just as in the De Dietrich 100 gallon system. The second involved the use of only the retreat blade impeller in the vessel, with no baffles. Figure 2.4 displays the hemispherical ChemGlass vessel with the unbaffled configuration.



Figure 2.4 ChemGlass hemispherical bottom vessel with no baffling.

2.2.3 Experimental Methods: LDV Velocity Measurement

Laser-Doppler Velocimetry (LDV) is a non-intrusive experimental method used to determine the local velocity distribution (including its fluctuating component) in a fluid inside any transparent piece of equipment. LDV has proven to be a highly effective experimental method for fluid dynamic studies and has been extensively used by several investigators [7, 26, 27, 28, 29, 30, 31] to quantify the flow characteristics of mixing vessels and reactors.



Figure 2.5 Schematic of laboratory LDV experimental set-up.

A Dantec 55X series Laser Doppler Velocimetry (LDV) apparatus (Dantec Measurement Technology USA, Mahwah, NJ, USA) was used here to determine the velocity flow field and turbulence intensity inside the vessel. A schematic of the LDV apparatus is given in Figure 2.5. The LDV system contained a 750 mW argon-ion laser (Ion Laser Technology, Inc.) producing a single multicolored laser beam passing through an optical filter to generate a monochromatic green beam (wavelength: 512 nm). The resulting beam passed through a beam splitter from which two beams emerged, one of which was passed through a Bragg cell to lower the frequency by 40 MHz and distinguish between positive and negative velocity measurements. The beams then

passed through a beam expander system and a final focusing lens with a focal length of 330 mm. This lens made the beams converge so that they intersected each other to form a small control volume in the interrogation region where the velocity was to be measured. In an actual measurement, the beams were made to converge inside either the flat-bottom glass vessel or ChemGlass hemispherical bottom vessel. The water in the glass vessel was seeded with neutrally buoyant 10 μ m silver coated particles (Dantec Measurement Technology USA, Mahwah, NJ, USA) that could follow the fluid flow pattern very closely.

The ChemGlass hemispherical bottom vessel was suspended from a bracket designed for this purpose, so that it could be placed in an external acrylic square tank filled with water, in order to minimize optical distortion during LDV measurements. The flat-bottom vessel simply rested at the bottom of the external acrylic square tank. The glass vessel/acrylic tank assembly was mounted on an x-y-z traversing system that enabled the velocity to be measured everywhere within the vessel. The light scattered by the particles was collected by a photodetector assembly placed next to the tank at a 90° orientation with respect to the laser (Figure 2.5), and connected to a data acquisition system configured so as to take 5000 measurements over a period of 60 seconds or less, at the same location. Data analysis was performed to generate the local mean and fluctuating velocity components in the direction parallel to that of the plane of the two laser beams. Appropriate rotation of the laser beam assembly and translation of the glass vessel/acrylic tank assembly yielded the velocity components in all three directions at any location.

As shown in Figure 2.6, seven iso-surfaces at different vertical (z) positions (z = 22 mm, z = 24 mm, z = 26 mm, z = 78 mm, z = 96 mm, z = 146 mm, z = 185 mm) were chosen where the local velocities were experimentally measured. The z = 0 location is the location at the bottom of each glass vessel (flat-bottom and ChemGlass hemispherical bottom, Figure 2.6).



Figure 2.6 Iso-surfaces investigated by LDV experimental measurements.

In the case of the flat-bottom vessel, LDV measurements were made at ten selected positions at different radial distances on each of the top three and bottom three iso-surfaces. Because of the presence of the impeller blades, measurements were made at only four locations on the iso-surface at z = 78 mm.

Similarly, in the case of the ChemGlass hemispherical bottom vessel, LDV measurements were made at ten selected positions at different radial distances on each of

the top three iso-surfaces. Because of the hemispherical shape of the vessel bottom and the presence of the impeller blades, measurements were made at only three locations on the iso-surface at z = 78 mm, and at six locations on the three lowest iso-surfaces.

At each measurement point, the three velocities components (tangential, axial, and radial) were obtained by LDV. The data acquisition time interval for each measurement was typically 60 seconds. In most cases, some 600 to 22000 instantaneous velocity data points were collected, from which the local average velocity and turbulence intensity could be calculated. The data rates were between 10 Hz to 370 Hz for most measurements.

2.3 Computational Fluid Dynamics (CFD) Modeling Methods

Computational Fluid Dynamics (CFD) is a computational tool designed to solve the momentum and mass balance equations under laminar or turbulent regimes to predict the flow field in complex geometries (such as mechanically stirred mixing vessels). CFD computations are typically conducted on mainframe computers or dedicated workstations. Numerical simulations of the velocity distribution and turbulence levels inside the stirred tank reactor system equipped with a retreat blade impeller will be conducted using a commercial mesh generator (Gambit 2.3.16) coupled with a CFD package (Fluent 6.3.26). The full 360°-tank geometry was incorporated in the simulations. The exact geometry of each component of the system (such as the glass vessel, impeller shaft, impeller blades, baffle, etc.) was obtained by measuring the actual dimensions of the actual component with a Vernier caliper. The geometry data then was inserted in the

mesh generator to get the exact shape of the volume in which the numerical CFD simulation was conducted.

The total system volume was separated into two separate volumes. These two volumes were created in order to use a multiple reference frame (MRF) simulation strategy with the symmetrical system cases and for a sliding mesh simulation strategy with the nonsymmetrical cases. The first volume enclosed the impeller region and the surrounding inner liquid volume. The second volume contained the baffle and remainder of the vessel volume. In order to control the grid size, separate sizing functions were created on various geometric faces such as the impeller blade, shaft, hub, baffle, and tank wall faces. A tetrahedral mesh (T-Grid) was created for each portion of the vessel volume. The meshing for all four simulation cases can be seen in Figure 2.7, and Table **2.2** summarizes their corresponding cell size information.



Figure 2.7 Isometric view of geometric mesh for: (a) unbaffled flat-bottom case, (b) single-baffle flat-bottom case, (c) unbaffled hemispherical-bottom case, (d) single-baffle hemispherical-bottom case.

 Table 2.2 Geometric mesh information for each simulation case.

	Cells	Faces	Nodes
Case 1: Unbaffled Flat-Bottom	336,057	741,064	69,053
Case 2: Single-baffle Flat-Bottom	210,623	450,548	40,514
Case 3: Unbaffled Hemispherical Bottom	256,532	565,374	53,511
Case 4: Single-baffle Hemispherical Bottom	344,389	742,659	68,788

The equiangle skew parameter was used to quantify the quality of mesh (0-best; 1-worst). Significant attention was paid to the generation of a high quality mesh, since this determined whether the simulation converged to a stable solution or not. The average value of the equiangle skew parameter was typically in the range 0.3 to 0.4, which is associated with a high-quality mesh. Individual cells (typically only a few) could have higher valued of this parameter, which was always smaller than 0.86 in both unbaffled cases and 0.94 in both single-baffle cases.

CFD programs such as Fluent numerically solve the general equations representing the conservation of mass and momentum. In Cartesian coordinates, the continuity equation for an incompressible fluid written using the summation convention can be written as:

$$\frac{\partial u_i}{\partial x_i} = 0 \tag{1}$$

Similarly, the momentum balance equation for the same incompressible fluid (Navier-Stokes equation) can be written as:

$$\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} = -\frac{1}{\rho} \frac{\partial P}{\partial x_i} + \nu \nabla^2 u_i + g_i$$
(2)

In this equation, the second term on left hand side accounts for the convective momentum transport, while the terms on the right hand side represent, respectively, pressure forces, viscous transport, and body forces, such as gravity.

In turbulent flow, it is customary to assume that the velocity at any point can be taken to be the sum of the mean (time-averaged) and fluctuating components, i.e.:

$$u_i = \overline{u}_i + u_i' \tag{3}$$

Using this equation the continuity equation can be rewritten as:

$$\frac{\partial \overline{u}_i}{\partial x_i} = 0 \tag{4}$$

and the time-averaged momentum equation, which can be used for the prediction of the velocities in turbulent flow, becomes:

$$\frac{\partial \overline{u}_{i}}{\partial t} + \overline{u}_{j} \frac{\partial \overline{u}_{i}}{\partial x_{j}} = -\frac{1}{\rho} \frac{\partial \overline{P}}{\partial x_{i}} + \nu \nabla^{2} \overline{u}_{i} + g_{i} - \frac{\partial}{\partial x_{j}} \left(\overline{u_{i}' u_{j}'} \right)$$
(5)

The last term in this equation represents the Reynolds stresses containing the product of the fluctuating velocity components. Since the Reynolds stresses cannot be predicted from first principles, they are typically calculated by making some assumptions about their relationship with other variables (closure problem). A number of different turbulence models are available for this purpose. Software packages such as Fluent offer different models to solve the closure problem [32].

2.3.1 Turbulence Models

A number of different turbulence models were used here to account for the turbulent effects during the numerical simulations. These models were the standard k- ε model, the RNG k- ε model, the realizable k- ε model, and the standard k- ω model. All three turbulence k- ε models have similar forms, with transport equations for k and ε . The major differences in the standard, RNG, and realizable k- ε models are as follows:

- the method of calculating turbulent viscosity
- the turbulent Prandtl numbers governing the turbulent diffusion of k and ε
- the generation and destruction terms in the ε equation.

The transport equations, methods of calculating turbulent viscosity, and model constants are presented separately for each model. The features that are essentially common to all models follow, including turbulent production, generation due to buoyancy, accounting for the effects of compressibility, and modeling heat and mass transfer [32].

2.3.1.1 Standard *k*-ε Turbulence Model

The standard k- ε model is a semi-empirical model based on model transport equations for the turbulence kinetic energy (k) and its dissipation rate (ε) [32]. The model transport equation for k is derived from the exact equation, while the model transport equation for ε was obtained using physical reasoning and bears little resemblance to its mathematically exact counterpart [32]. In the derivation of the standard k- ε model, it was assumed that the flow is fully turbulent, and the effects of molecular viscosity are negligible. The standard k- ε model is therefore valid only for fully turbulent flows. Its main advantages are that it is robust and computationally economical [32].

The governing equations for standard k- ε model are [32]:

$$\frac{\partial}{\partial t}(\rho k) + \frac{\partial}{\partial x_{i}}(\rho k u_{i}) = \frac{\partial}{\partial x_{j}} \left[\left(\mu + \frac{\mu_{i}}{\sigma_{k}} \right) \frac{\partial k}{\partial x_{i}} \right] + G_{k} + G_{b} - \rho \varepsilon - Y_{M} + S_{k}$$
(6)
$$\frac{\partial}{\partial t}(\rho \varepsilon) + \frac{\partial}{\partial x_{i}}(\rho \varepsilon u_{i}) = \frac{\partial}{\partial x_{j}} \left[\left(\mu + \frac{\mu_{i}}{\sigma_{\varepsilon}} \right) \frac{\partial \varepsilon}{\partial x_{j}} \right] + C_{1\varepsilon} \frac{\varepsilon}{k} (G_{k} + C_{3\varepsilon} G_{b}) - C_{2\varepsilon} \rho \frac{\varepsilon^{2}}{k} + S_{\varepsilon}$$
(7)

2.3.1.2 RNG k-E Turbulence Model

The RNG k- ε model was derived using a rigorous statistical technique (called renormalization group theory) [32]. It is similar in form to the standard k- ε model, but includes the following refinements:

• The RNG model has an additional term in its ε equation that significantly improves the accuracy for rapidly strained flows.

- The effect of swirl on turbulence is included in the RNG model, enhancing accuracy for swirling flows.
- The RNG theory provides an analytical formula for turbulent Prandtl numbers, while the standard k- ε model uses user-specified, constant values.
- While the standard k-ε model is a high-Reynolds-number model, the RNG theory provides an analytically-derived differential formula for effective viscosity that accounts for low-Reynolds-number effects. Effective use of this feature does, however, depend on an appropriate treatment of the near-wall region.

These features make the RNG k- ε model more accurate and reliable for a wider class of flows than the standard k- ε model [32].

The RNG-based k- ε turbulence model is derived from the instantaneous Navier-Stokes equations, using a mathematical technique called "renormalization group" (RNG) methods [32]. The analytical derivation results in a model with constants different from those in the standard k- ε model, and additional terms and functions in the transport equations for k and ε [32].

The governing equations for RNG k- ε model are [32]:

$$\frac{\partial}{\partial t}(\rho k) + \frac{\partial}{\partial x_i}(\rho k u_i) = \frac{\partial}{\partial x_j}\left(\alpha_k \mu_{\text{eff}} \frac{\partial k}{\partial x_j}\right) + G_k + G_b - \rho \varepsilon - Y_M + S_k$$
(8)

$$\frac{\partial}{\partial t}(\rho\varepsilon) + \frac{\partial}{\partial x_{i}}(\rho\varepsilon u_{i}) = \frac{\partial}{\partial x_{j}}\left(\alpha_{k}\mu_{\text{eff}}\frac{\partial\varepsilon}{\partial x_{j}}\right) + C_{1\varepsilon}\frac{\varepsilon}{k}(G_{k} + C_{3\varepsilon}G_{b}) - C_{2\varepsilon}\rho\frac{\varepsilon^{2}}{k} - R_{\varepsilon} + S_{\varepsilon}$$

(9)

2.3.1.3 Realizable *k*-ε Turbulence Model

The realizable k- ε model is one of the variant of standard k- ε model. It is called "realizable" because the model satisfies certain mathematical constraints on the normal stresses, consistent with the physics of turbulent flows [32]. It is suitable for complex shear flows involving rapid strain, moderate swirl, vortices and locally transitional flows [32]. It is more accurate compared with standard k- ε model, and it typically converges readily [32]. The governing equations for Realizable k- ε model are [32]:

$$\frac{\partial}{\partial t}(\rho k) + \frac{\partial}{\partial x_{i}}(\rho k u_{j}) = \frac{\partial}{\partial x_{i}} \left[\left(\mu + \frac{\mu_{i}}{\sigma_{k}} \right) \frac{\partial k}{\partial x_{j}} \right] + G_{k} + G_{b} - \rho \varepsilon - Y_{M} + S_{k}$$
(10)
$$\frac{\partial}{\partial t}(\rho \varepsilon) + \frac{\partial}{\partial x_{j}}(\rho \varepsilon u_{j}) = \frac{\partial}{\partial x_{j}} \left[\left(\mu + \frac{\mu_{i}}{\sigma_{\varepsilon}} \right) \frac{\partial_{\varepsilon}}{\partial x_{j}} \right] + \rho C_{1} S \varepsilon - \rho C_{2} \frac{\varepsilon^{2}}{k + \sqrt{v \varepsilon}} + C_{1\varepsilon} \frac{\varepsilon}{k} C_{3\varepsilon} G_{b} + S_{\varepsilon}$$
(11)

2.3.1.4 Standard *k*-ω Turbulence Model

The standard $k-\omega$ model is an empirical model based on model transport equations for the turbulence kinetic energy (k) and the specific dissipation rate (ω), which can also be thought of as the ratio of ε to k [32].

Since the $k-\omega$ model has been modified over the years, production terms have

been added to both the k and ω equations, which have improved the accuracy of the model for predicting free shear flows [32]. It has lower sensitivity to boundary conditions [32]. It has good performance for free shear and low Reynolds number flows [32]. The governing equations for the standard k- ω model are [32]:

$$\frac{\partial}{\partial t}(\rho k) + \frac{\partial}{\partial x_i}(\rho k u_i) = \frac{\partial}{\partial x_j}\left(\Gamma_k \frac{\partial k}{\partial x_j}\right) + G_k - Y_k + S_k$$
(12)

$$\frac{\partial}{\partial_{i}}(\rho\omega) + \frac{\partial}{\partial x_{i}}(\rho\omega u_{i}) = \frac{\partial}{\partial x_{j}}\left(\Gamma_{\omega}\frac{\partial\omega}{\partial x_{j}}\right) + G_{\omega} - Y_{\omega} + S_{\omega} \quad (13)$$

2.3.2 Additional Computational Details

Simulations were carried out on a Dell Precision 650 Workstation, equipped with two Intel XEON 3.4 Gigahertz processors and 3.25 gigabytes of random access memory (RAM). A typical computational run to calculate the flow field in the entire reactor for a multiple reference frame simulation took some 30-60 hours, depending on the different cases and number of cells. For a sliding mesh simulation, a typical computational run took around 2 weeks to complete.

CFD simulations were carried out for all four experimental cases. For each of the simulations, a meshed grid was constructed using Gambit 2.3.16, and the strategy described earlier in Section 2.1.4. The geometry of the vessel, impeller, and baffle all matched the actual experimental equipment. The mesh files were used to conduct simulations through Fluent 6.3.26. An agitation speed of 100 RPM, corresponding to an impeller tip speed of 1.10 m/s, and an impeller Reynolds number of 81,920, was used in all simulations and accompanying experiments. Multiple turbulence models were used in all four cases, but the RNG k- ε turbulence model was only one used in all four cases.

2.4 Results

2.4.1 Velocity Profile for the Unbaffled, Flat-Bottom Tank

Three CFD simulations were completed for the case of the unbaffled, cylindrical flatbottom tank using a multiple reference frame strategy and the RNG k- ε , standard k- ε , and standard k-a turbulence models as described in Section 2.1.4. Two separate LDV experimental studies were conducted for this case. The first experimental study was conducted by the author of this study using the experimental system described in Section 2.1.3.1. A total of 10 velocity measurements, each one including all three velocity components, were obtained in the first experimental study for this case. The second experimental study was conducted by a recent Pharmaceutical Engineering Masters Graduate, Deepak Madhrani, using a slightly modified experimental system with a fiber optic probe as part of the transmitting and receiving optics and a back-scattering method for collection of scattered laser light [33]. A total of 13 velocity measurements, each one including all three velocity components, were obtained in the second experimental study for this case [33]. All these CFD simulation and LDV experimental results are presented in Appendix A.1 (Figures A.1.1.1-A.1.3.4). An example of the typical tangential velocities measured on the iso-surface at z/H = 0.33 is shown in Figure 2.8. In general, the flow field in this type of configuration is dominated by a high tangential velocity component, especially above the impeller. Figure 2.8 shows that the tangential velocity on this plane is typically 40 to 50% of the impeller tip speed and it extends for a significant portion the entire iso-surface. The magnitude of the tangential component of the velocity was found to be midways between the shaft and the wall, which could be an

ideal location for placing a baffle. There is a considerable agreement between the two LDV experimental results, but there is a discrepancy between the predicted CFD simulation results and the LDV experimental results. While both the CFD and LDV results reach the same 40 to 50% of the impeller tip velocity, the CFD results show the maximum velocity occurring closer to the tank wall.



Figure 2.8 Comparison between LDV data and CFD prediction for tangential velocities at iso-surfaces z = 96mm in the unbaffled, cylindrical flat-bottom tank. Error bars represent the standard error from 3 replicate experiments.

By comparison, the axial and radial components of the fluid velocity, also presented in detail in Appendix A.1, were found to be very low. Example of the typical profiles for these velocity components are shown in Figure 2.9 and Figure 2.10, respectively (in all figures positive axial velocities point upward, and positive radial velocities point outwards, toward the wall). In most cases, the axial components were found to be in the range of 0-10% of the impeller tip speed. In the region above the impeller, the axial component of the velocity was found to be positive between the wall and impeller blade region. In the upper portion of the tank, higher axial velocities were observed near the shaft due to the presence of a vortex. Axial velocities between the center and the wall had higher negative magnitudes, indicating a downward movement of the fluid. There is generally a good agreement between the two LDV experimental axial velocity results from the center of the tank to a radial distance of around 0.5. However, at radial distances above 0.5, discrepancies between the two LDV experimental axial velocity results appear. Similar to the tangential velocity results, there is a discrepancy between the predicted CFD simulation results and the LDV experimental results, but it is not as pronounced in these figures. Both the CFD and LDV results reach the same 0 to 10% of the impeller tip velocity range, but a lot of the discrepancies occur between a radial distance of around 0.5 and the tank wall.



Figure 2.9 Comparison between LDV data and CFD prediction for axial velocities at iso-surfaces z = 96mm in the unbaffled, flat-bottom tank. Error bars represent the standard error from 3 replicate experiments.

The radial velocities measured here ranged from 0 to 5% of the tip speed. Above the impeller region, radial component was almost negative everywhere confirming the movement of the fluid towards the shaft. In the region below the impeller, the radial velocity components had a positive magnitude, indicating that the fluid movement is towards the wall. Similar to the axial velocity results, there is generally a good agreement between the two LDV experimental radial velocity results from the center of the tank to a radial distance of around 0.5. However, at radial distances above 0.5, discrepancies between the two LDV experimental radial velocity results appear. Similar to the axial velocity results appear. Similar to the axial velocity results appear to the tank to the tank to the tank to LDV experimental radial velocity results appear. Similar to the axial velocity results, the discrepancy between the predicted CFD simulation results and the LDV experimental results is not as pronounced in these figures as in the

tangential velocity figures. Both the CFD and LDV results reach the same 0 to 5% of the impeller tip velocity range, but a lot of the discrepancies occur between a radial distance of around 0.5 and the tank wall.



Figure 2.10 Comparison between LDV data and CFD prediction for radial velocities at iso-surfaces z = 96mm in the unbaffled, flat-bottom tank. Error bars represent the standard error from 3 replicate experiments.

By examining the whole set of velocities presented in Appendix A.1 for this case, one can see that the overall flow is largely dominated by a strong swirling tangential flow which ramps up rapidly from very near zero at the shaft to up to 50% of the tip speed at a radial distance of about 0.4. The dominant tangential flow is also visualized in the velocity vector images shown in Figure 2.11. All velocity vector images from the CFD simulation results for this case are presented in Appendix B.1 (Figures B.1.1-B.1.4). In the rest of the tank, the tangential flow is nearly constant before dropping at the wall. By

contrast, the axial velocities are typically much smaller, indicating poor top-to-bottom recirculation, and the radial velocities are even smaller. The weak axial flow is typically directed downward in the middle of the tank and upward near the wall, as expected. The LDV experimental results seem to have a closer affinity to the CFD simulation results of the multiple reference frame, RNG k-ε turbulence model simulation.





2.4.2 Velocity Profile for the Single-Baffle, Flat-Bottom Tank

Three CFD simulations were completed for the case of the single-baffle, cylindrical flatbottom tank using a multiple reference frame strategy and the RNG k- ε turbulence model. and a sliding mesh strategy and the RNG k- ε and realizable k- ε turbulence models as described in Section 2.1.4. Two separate LDV experimental studies were conducted for this case, similar to the unbaffled case. The velocity profiles for the case of the singlebaffle, cylindrical, flat-bottom tank are shown in Figures A.2.1.1-A.2.3.4, representing the comparison of the three CFD simulations and two LDV experimental studies. All three velocity components are represented in these velocity profiles. A typical example of the velocity profiles is shown in Figures 2.12 and 2.13. These figures show that the tangential velocity profile is now typically relatively flat, with velocities on an order of magnitude of about 25-30% of the tip speed, i.e., much smaller than in the unbaffled case. This implies that partial baffling had a significant effect on the tangential component of the velocity, for which the magnitudes were reduced by almost 40% of those obtained in the unbaffled configuration. The dominant tangential flow is also visualized in the velocity vector images shown in Figure 2.14 below. All velocity vector images from the CFD simulation results for this case are presented in Appendix B.2 (Figures B.2.1-B.2.6).

In addition, the baffled system showed stronger radial and axial components of the velocity as compared to the unbaffled configuration, with velocity components in the range 0-14% of the tip speed. The higher magnitudes were obtained above the impeller region, near the shaft. These data show a more directional axial flow than in the previous case, with an upward flow near the tank wall, and a downward flow in the central region.
The radial component of the velocity was found to be nearly always negative except in the impeller region. This is consistent with the typical flow produced by a radial impeller in a baffled tank, where the fluid is pushed radially outward toward the wall near the impeller blades, and recirculated back toward the center anywhere else in the

tank.



Figure 2.12 Comparison between LDV data and CFD prediction for tangential velocities at iso-surfaces z = 96mm in the single-baffle, flat-bottom tank. Error bars represent the standard error from 3 replicate experiments.



Figure 2.13 Comparison between LDV data and CFD prediction for axial and radial velocities at iso-surfaces z = 96mm in the single-baffle, flat-bottom tank. Error bars represent the standard error from 3 replicate experiments.



Figure 2.14 Front view and side view of velocity vectors from CFD simulation at isosurface rz-plane ($\theta = 0, \theta = \pi$) in the single-baffle, flat-bottom tank.

2.4.3 Velocity Profile for the Unbaffled, Hemispherical-Bottom Tank

One CFD simulations was completed for the case of the unbaffled, cylindrical hemispherical-bottom tank using a multiple reference frame strategy and the RNG k- ε turbulence model as described in the previous section. Only the LDV experimental study by Madhrani was conducted for this case [33]. The velocity profiles for the case of the

unbaffled, cylindrical, hemispherical-bottom tank are shown in Figures A.3.1.1-A.3.2.3. Typical examples of the velocity profiles are shown in Figures 2.15 and 2.16. The velocity profiles obtained for the case of the unbaffled, hemispherical-bottom tank were similar to that of the unbaffled, flat-bottom tank except in the region below the impeller. The velocity vector images from the CFD simulations results for this case are presented in Appendix B.3 (Figures B.3.1-B.3.5). Figure 2.17 below displays a typical example of the velocity vectors.

The tangential component of the velocity observed in this case was clearly strong and had a similar magnitude as that obtained in the case of unbaffled flat-bottom tank. The maximum tangential velocity was obtained at the center of the shaft and tank wall, which again seems to be the best location for baffling. Above the impeller region, axial component of the velocity of the component of the velocity had higher negative magnitudes between the center and the wall, which again confirms the downward motion of the fluid.

Below the impeller, the axial component of the fluid velocity was generally very weak except near the wall where a slightly stronger axial velocity in the downward direction was observed. This indicates that this region is somewhat poorly mixed and possibly segregated from the rest of the tank.

The radial velocities for this configuration were very hard to collect and the results were of poor quality (low data acquisition rate) and showed a poor degree of reproducibility. This is likely the result of the curvature of the tank, especially in the hemispherical portion of the tank, which, in the worst cases, refracted the beams to the

point of preventing them from intersecting. Therefore, the data for this velocity component are not shown for this case.

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Figure 2.15 Comparison between LDV data and CFD prediction for tangential and axial velocities at iso-surfaces z = 22mm in the unbaffled, hemispherical-bottom tank. Error bars represent the standard error from 3 replicate experiments.



Figure 2.16 Comparison between LDV data and CFD prediction for axial velocities at iso-surfaces z = 185mm in the unbaffled, hemispherical-bottom tank. Error bars represent the standard error from 3 replicate experiments.



Figure 2.17 Front view and side view of velocity vectors from CFD simulation at isosurface rz-plane in the unbaffled, hemispherical-bottom tank.

2.2.4 Velocity Profile for the Single-Baffle, Hemispherical-Bottom Tank

Three CFD simulations were completed for the case of the single-baffle, cylindrical hemispherical-bottom tank using a multiple reference frame strategy and the RNG k- ϵ turbulence model, and a sliding mesh strategy and the RNG k- ϵ and realizable k- ϵ turbulence models as described in Section 2.1.4. Only the LDV experimental study by

Madhrani was conducted for this case [33]. The velocity profiles for the case of the single-baffle, cylindrical, hemispherical-bottom tank are shown in Figures A.4.1.1-A.4.2.3, and examples are presented in Figure 2.18. The velocity profiles obtained for the baffled, hemispherical-bottom tank has a lower tangential component of the velocity than the unbaffled case, as one can anticipate. The magnitude of the tangential velocity dropped significantly and was around 45% lower than that obtained in the unbaffled configuration. A comparison with the date obtained for the baffled, flat-bottom case; show that the velocity probates, both tangential and radial, in the upper portion of the tank are similar in both baffled cases. However, below the impeller, the presence of a different type of bottom results in different velocity profiles, especially in the axial direction. No radial data could be collected because of the problem generated by the curvature of the tank bottom. The velocity vector images from the CFD simulations results for this case are presented in Appendix B.4 (Figures B.4.1-B.4.6). Figure 2.19 below displays a typical example of the velocity vectors.



Figure 2.18 Comparison between LDV data and CFD prediction for tangential and axial velocities at iso-surfaces z = 185mm in the single-baffle, hemispherical-bottom tank. Error bars represent the standard error from 3 replicate experiments.



Figure 2.19 Front view and side view of velocity vectors from CFD simulation at isosurface rz-plane ($\theta = 0, \theta = \pi$) in the single-baffle, hemispherical-bottom tank.

2.5 Discussion

The experimental data obtained in this work confirm that the flow in the unbaffled tank is dominated by the tangential velocity to a more significant extent than the baffled tank, irrespective of the shape of the tank bottom, which is what one would expect in such a case. In addition, the axial component of the velocity is larger in the baffled tank than in the unbaffled tank but only in the upper portion of the tank where the baffle is present. Below the impeller, where no baffling exists, the axial velocity profiles are rather weak with or without the baffle, indicating relatively little top to bottom recirculation in this critical region of the tank. The radial velocities are generally weak, with or without baffle, but the presence of the baffle changes the direction of the weak flow pattern depending on the location.

As already mentioned, little information is available in the literature on these systems. Even the few studies currently available [3, 4, 5, 6, 7, 8, 9] did not produce the same kind and volume of information produced here. For example, Reilly et al. (2007) investigated a small, conical-bottom tank with a relatively large and thick impeller that would not be scalable to a full-scale system. In addition, these authors, as well as nearly all other authors who looked at somewhat similar system, did not conduct any experimental determination of the velocity distribution in their systems, but almost exclusively carried out computational studies with no experimental, direct velocity verification. Furthermore, most of the few reports available in the literature did not examine systems similar to that investigated here, but instead examined impeller-tank systems with relative dimensions that are quite different from a scaled down version of an industrial reactor, as it is the case here.

The experimental data obtained in this work can be compared with the experimental results obtained by Deepak Madhrani (2008) in this laboratory using a slightly different LDV system with a different receiver operating in a back-scattering mode [33]. The results can also be compared with Computational Fluid Dynamics (CFD) simulation results. Such comparisons are shown in detail in Appendix A, and in Figures 2.8, 2.9, 2.10, 2.12, 2.13, 2.15, 2.16, and 2.18 in Sections 2.2.1 – 2.2.4. The comparison between the experimental data of this work and Madhrani's experimental data show, in general, good agreement, especially as far as the dominating tangential component of the velocity is concerned. When the data are compared with CFD predictions, the agreement is also rather favorable, especially for the tangential velocities in baffled systems, but less so for the unbaffled system. However, there are discrepancies between the two experimental studies and the CFD predictions when comparing the axial and radial components of the velocity.

As seen in the figures found in Sections 2.2.1 - 2.2.4 and Appendix A (Sections A.1.2.1 - A.1.3.4, A.2.2.1 - A.2.3.4, A.3.2.1 - A.3.2.3, and A.4.2.1 - A.4.2.3), considerable errors exist in the agreement of the LDV experimental results and the CFD predictions of the axial and radial components of the velocity. These errors could be due to the typically low magnitudes of the axial and radial velocities in these systems, and thus magnifying experimental error effects. Large flow instabilities in the axial and radial velocity directions exist compared to the corresponding velocity magnitude due to weak flow and large velocity fluctuations. As described in Section 2.1.3.1, a typical LDV measurement is the average of thousands instantaneous velocity measurements over tens of seconds or a minute. The mean velocities measured by the LDV experiments are

averages of small but highly fluctuating values when measuring velocity in the axial and radial directions of these systems. Thus, LDV measurements do not capture the flow instabilities very well. This is even magnified further by poor LDV data acquisition rates found in low velocity regions like below the impeller. This is a possible reason why the magnitude of the errors is not constant, as the degree of the discrepancy varies throughout the vertical (z) and radial (r) locations within the reactor vessels, and the highest degree of error can be found below the impeller, where the axial and radial velocities are at their lowest magnitude.

Other experimental issues that contribute to the error come as a result of the absence of significant tank baffling in these systems. The absence of significant tank baffling makes the flow highly sensitive to the exact geometry of the system. Thus, if small geometric differences between the ideal tank used in the simulation and the actual experimental systems exist, the comparison of the results would be poor due to the amplification of the differences of weak, small velocities in the axial and radial directions. Care was always taken when experiments were conducted, but even the slightest human error could affect the results.

The final possibility of the error could be due to plotting axial and radial velocities at constant z/H locations (i.e., on horizontal planes). This may amplify discrepancies between data and simulation results if axial location of recirculation patterns are not precisely captured by the simulations. Figure 2.20 below displays a comparison of the LDV and CFD results of the single-baffle, cylindrical flat-bottom tank case at three different vertical locations below the impeller (z/H = 0.0766, 0.0836, 0.090). The region selected in the figure ranges only 4 mm in height and is located at an

important recirculation section of the system. The CFD velocity profiles appear to be almost identical between these three locations for both the axial and radial component. However, the LDV velocity profiles show significant discrepancies, and their flow directions are not even the same at certain locations. This implies that a recirculation exists in this region which the LDV results have captured, but the CFD simulation results have not. In addition, it is likely that the flow in this region is affected by small geometric differences, such as those that can be inadvertently generated by even the slightest misalignment of the impeller with respect to the centerline or the vessel.

2.6 Impact of Fluid Dynamic Results on the Optimal Location of the Impinging Jets Within The Stirred-Tank Reactor

The simulation and experimental results of this chapter aided in the decision of the location of the impinging jets within the stirred-tank reactor in Chapter 3. The motivation was to locate the jets in the area of highest mixing intensity in order to provide the most energy to the crystallization process. It was determined that the best location in a glass-lined reactor system with a retreat blade impeller would be on the same radial plane as the impeller tip. This is due to the fact that a retreat blade impeller is a radial type impeller, and Figure 2.21 below displays the optimum location for the jets.



Figure 2.20 Comparison between LDV data and CFD prediction for axial and radial velocities at iso-surfaces z = 22mm, z = 24mm, and z = 26mm in the single-baffle, flat-bottom tank. Error bars represent the standard error from 3 replicate experiments.

2.7 Conclusions for this Chapter

A significant amount of fluid velocity data was collected with an LDV system for unbaffled and partially baffled tank reactors provided with a retreat-blade impeller. In both cases, two systems were studied, i.e., one with a flat-bottom tank and another with a hemispherical-bottom tank. In all the systems investigated here, the tangential component of the velocity appears to dominate the flow over the axial and radial components. The highest tangential velocity is typically about 35% of the impeller tip speed for the baffled case and about 47% of the impeller tip speed for the unbaffled case, irrespective of the type of tank bottom. The axial component of the velocity was always significantly smaller than the tangential component, and was on the order of 5-15%, with the higher value obtained in the baffled configuration. The radial component of the velocity was found to be the smallest of the three, with velocity magnitudes ranging from 0-10%. The presence of a hemispherical bottom instead of a flat bottom did not significantly alter the velocity profiles above the impeller, when similarly baffled systems were compared. However, this was not entirely the case below the impeller, where the presence of the hemispherical bottom resulted in a slightly larger down-flow next to the wall. The dominance of the tangential velocity and the small value of the radial and especially axial velocity in all the system investigated here indicate a poor vertical recirculation of the fluid inside the tank and therefore a reduced mixing efficiency for this type of reactors.

The experimental results obtained in this work compare favorably with the experimental results and the computational predictions obtained previously in this laboratory. However, discrepancies exist in the axial and radial components of the

velocity due to their small magnitudes and the systems' high sensitivity. The small velocity magnitudes in the axial and radial directions amplify this error.

Together with recent data obtained in this laboratory, the data presented here constitute the first detailed mapping of the flow distribution inside a system of significant industrial importance that has not been studied to any significant extent before. It is expected that this work can contribute to a better understanding of the way in which these reactors operate and help their users operate them more effectively.

Finally, the results of fluid dynamic simulation and experimental results obtained here helped identify the optimal location of the impinging jets within the stirred-tank reactor. Accordingly, the best location in a glass-lined reactor system with a retreat blade impeller where the jets should be located would be on the same radial plane as the impeller tip, where the fluid velocity and turbulence dissipation rate (ε) were at its greatest.



Figure 2.21 The optimum location for the impinging jets according to the fluid dynamic study of the retreat blade system.

CHAPTER 3

CRYSTAL PRECIPITATION WITHIN SONICATED SUBMERGED IMPINGING JETS MIXING SYSTEM

3.1 Background

This component of the project was focused on the formation of micron- and nano-sized particles within a stirred-tank reactor setup similar to that described above. The idea was to utilize an impinging jet mixer placed inside a stirred tank in order to form these particles. The major material used here is a representative drug compound, or active pharmaceutical ingredient (API). The API selected for this study is Griseofulvin (Figure 3.1). Griseofulvin ($C_{17}H_{17}ClO_6$) is an orally administered, anti-fungal drug that is currently produced by different companies [34]. The drug is used to treat ringworm infections of the skin and nails in both animals and humans [34]. Griseofulvin was chosen to be a representative of a Biopharmaceutics Classification System (BCS) class IV drug and how such a class of drugs behaves with our experimental system. It is highly hydrophobic (water solubility less than 0.2 mg/mL at 25 °C [35]), and is known to have a highly variable bioavailability (25% to 70%) when microsized [36].



Figure 3.1 Chemical structure of Griseofulvin [37].

Griseofulvin is slightly soluble in various organic solvents, including acetone, dimethylformide (DMF), dichloromethane (DCM), and triacetin. Griseofulvin is more soluble in DMF (77.52 mg/mL at 29 °C) and DCM (219.92 mg/mL at 24 °C) than the other two solvents according to a preliminary investigation conducted by a parallel study group at Rutgers University in Piscataway, NJ [38]. Since DMF and DCM are toxic, acetone and triacetin were chosen as potential solvents to use in this study. Griseofulvin has shown to have a higher solubility in acetone (38.6 mg/mL at 29 °C) than in triacetin (15.27 mg/mL at 29 °C). Thus acetone was selected as the solvent for Griseofulvin in this work.

Since griseofulvin is highly hydrophobic, water was chosen as the anti-solvent for this study. Depending on the experiment, the anti-solvent solution was either pure water or water added with various surfactants and polymers to control particle size and particle agglomeration. The selection of these surfactants and/or polymers was influenced by the work and recommendations of Dr. Somenath Mitra and his doctoral student Xiangxin Meng of the Department of Chemistry and Environmental Science at NJIT. Polysorbate 80 (or commercially known as Tween[®] 80), sodium dodecyl sulfate (SDS), and hydroxypropyl methylcellulose (HPMC) (HY124, Hypromellose 2208, HPMC USP) were chosen for this study.

3.2 Experimental Materials, Equipment and Methods

3.2.1 Materials

The Griseofulvin used in this work was manufactured and donated by Johnson & Johnson. This material was originally prepared by Johnson & Johnson by milling, and

had a mean particle size of 13.56 µm although the crystals had wide size distribution and different shapes (as discussed in the Results section below). Acetone (technical grade, purity: 99+%, Acros Organics, Somerville, New Jersey) was the only solvent used to dissolve Griseofulvin prior to the precipitation experiments. Polysorbate 80 (Tween[®] 80) was purchased from Sigma-Aldrich Inc., St. Louis, Missouri (P-8074). SDS (ultrapure, Biomedicals LLC, Solon, Ohio), and HPMC (Spectrum Chemical Mfg. Corp., New Brunswick, New Jersey) were also purchased from commercial vendors. All aqueous antisolvent solutions were prepared with distilled water. The preparation methods for the drug solution and anti-solvent solution are described below in the section on Experimental Procedure.

3.2.2 Experimental Apparatus

The design of the impinging jet mixer experimental apparatus was based upon the Bristol-Myers Squibb Company patent by Lindrud et. al. [19]. Before the design was finalized, Dr. San Kiang and Dr. Soojin Kim of Bristol-Myers Squibb Company provided some key recommendations, which were incorporated in the design. 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 antisolvent solutions stored in feed tanks. Using the results from the fluid dynamics portion of the project in Chapter 2 as a guide, the location of the impinging jets within the stirred tank reactor was determined. Two different experimental systems were used for lower jet velocity (2.66 m/s) and higher jet velocity (15 m/s) experiments.

3.2.2.1 Experimental Set-up for Higher Jet Velocity Experiment

The experimental apparatus schematic for higher jet velocity is shown in Figure 3.2. Figure 3.3 displays an image of the actual apparatus in the laboratory. Two jacketed 1liter reservoirs contained the drug solution (Griseofulvin in acetone) and the anti-solvent solution (water plus HPMC and SDS) separately. The reservoir with the anti-solvent solution was jacketed and cooled by circulating cold water through jacket using an external water bath provided with a pump (Endocal RTE-110, Neslab Instruments Inc., Newington, New Hampshire). The drug solution did not have to be heated or cooled so the corresponding reservoir was not connected to any water bath.



Figure 3.2 Schematic of experimental impinging jets apparatus.



Figure 3.3 Actual impinging jets experimental apparatus used in laboratory.

Each reservoir was connected to a gear pump through recirculation loop; made of stainless steel piping; using ½ inch diameter tubing (HDPE), which then fed the impinging jet assembly downstream. These pumps were a Lobee 2LOE-S (Lobee Pump & Machinery Company, Gasport, New York) for the anti-solvent solution, and a Shertech GPST2 (Hypro Industrial Products Group, New Brighton, Minnesota) for the drug solution. The flow rates of each solution passing through the gear pumps were controlled by adjusting the recirculation flow around the gear pumps through respective globe valves (CF8M, ½ inch diameter, Sharpe Valves, Northlake, Illinois), as shown in Figures 3.2 and 3.3.

The impinging jet assembly consisted of two separate vertical stainless steel tubes (ID: 3.175 mm (1/8 inch); OD: 6.35 mm (1/4 inch)) connected at the top end to the pumps through $\frac{1}{2}$ inch HDPE tubing and at the bottom end to the impinging jet nozzles via 90° elbows (Figure 2.3). The jets are shown in Figure 3.4. The jets were made of

stainless steel and had internal diameters of 1.016 mm ID (1/25 inch) for the anti-solvent solution and 0.506 mm ID (1/50 inch) for the solvent solution. The OD of both nozzles was 1.59 mm, (i.e., 1/16 inch). They were held in place with a compression fitting stainless steel elbow with custom-made delrin collars. Two custom-made brackets (Figure 3.4) secured the stainless tubing feeding the jets within the main process vessel. These brackets not only kept the tubing from moving during experiments, but also allowed for 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. However, the location of the jets and the distance between the jets was kept constant in this study. The distance between two nozzles was 7 mm.



Figure 3.4 The two impinging jets with accompanying brackets within main process tank.

The nozzle assembly was mounted inside a jacketed receiving tank. Two different receiving tanks, 5 inch diameter (2 liter) and 8 inch diameter (5 liter) were used depending on the experiment. The receiving tank was cooled by circulating coolant through its jacket using circulatory pump (Cole-Parmer, 12108-20). The 8-inch diameter receiving tank was stirred by a 3-blade, retreat-blade impeller, 89 mm in diameter driven by a 1/8 HP motor (455479, G K Heller Corp., Floral Park, New York). The impeller clearance off the tank bottom was 35 mm. External stirring was not possible in case of smaller diameter tank due to insufficient space. The nozzles were facing each other at 180° and were place at about the same height as of impeller (i.e., closer to bottom of the tank).

A sonication probe was placed between two nozzles. The probe was connected to a 250 W sonicator (Omni-Ruptor 250, Omni International Inc., Marietta, Georgia). Two different sonication probes having diameter of 3.8 mm and 12.7 mm were used in different experiments in order to cover a wide range of sonication powers.

3.2.2.2 Experimental Set-up for Lower Jet Velocity Experiment

The experimental apparatus for the lower jet velocity (2.66 m/s) experiment is shown as a schematic in Figure 3.5 and as the actual apparatus in the laboratory in Figure 3.6. The reservoirs described in Section 3.2.2.1 were connected directly with two centrifugal pumps (KL3404, Baldor Industrial Motor, Sonoma, California, for anti-solvent solution and VL3507, Baldor Industrial Motor, Sonoma, California, for drug solution) using ¹/₄ inch diameter HDPE pipes (recirculation loop was not used to control the flow rate) and outlets of the pumps were connected to the impinging jet assembly using same ¹/₄ inch diameter HDPE tubing. The sizes of both the nozzles in the impinging jet assembly were the same as before (0.506 mm ID (1/50 inch) and 1.59 mm OD (1/16 inch). All other specifications were the same as described in the previous section.



Figure 3.5 Schematic of experimental impinging jets apparatus.



Figure 3.6 Actual impinging jets experimental apparatus used in laboratory.

3.2.3 Experimental Methods

3.2.3.1 Design of Experiments (DOE) Approach

The impinging jet mixer investigation involves a significant amount of experimental work. Though crystallization studies can be simulated using population balance modeling from various simulation programs such as Fluent [39, 40, 41, 42, 43], the key parameters behind the simulations (nucleation rate, growth rate, etc.) must be obtained through experimentation. The experimental apparatus and drug/solvent system chosen for this study have not yet been modeled. So the bulk of the study was conducted using an experimental approach. The strategy of this experimental study was developed using a Design of Experiments (DOE) approach.

DOE is a systematic approach to performing an investigation of a system or process [44]. In this case, the system is the impinging jet mixer. A series of structured experiments are designed in which planned changes are made to the input variables of the process or system [44]. The effects of these changes on an individual or series of predefined output(s) are then recorded. Then, a statistical assessment is performed on the results of the structured experiments [44].

A major advantage of a DOE approach is that it provides a formal method of maximizing information gained while limiting the resources required [44]. This is a key feature when faced with an investigation that cannot afford wasteful experiments that provide unusable data results [44]. It can provide a more reliable experience than "one-at-a-time" experimental methods [44]. DOE methods allow a judgment on the significance to the output of input variables acting alone, as well input variables acting in combination with one another [44]. This cannot be accomplished through "one-at-a-

time" experimentation [44]. "One-at-a-time" testing always carries the risk that the individual researcher may discover one input variable to have a significant effect on the output response, but fail to discover that changing another separate variable may alter the effect of the first variable [44]. This would be the case for a dependency or interaction between the variables [44]. The individual is fooled because of the temptation to stop the test when the first significant effect has been found [44]. In order to reveal an interaction or dependency, "one-at-a-time" testing heavily relies on the researcher luckily performing the tests in the appropriate direction [44]. However, DOE plans for all possible dependencies to begin with, and then prescribes exactly what data are needed to assess these relationships [44].

Every DOE project begins with identifying the input variables and the response (output) that is to be measured [44]. For each input variable, a number of levels are defined which correspond to the desired investigative range of the variable. The researcher should choose this range based upon the amount of treatments needed to decipher if any effect on other variables or the response exists [44]. Once the treatments for each input variable has been defined, an experimental plan is formed which tells the researcher where to set each experimental parameter for each run [44]. The researcher conducts each of these experiments and measures the corresponding response [44]. The method of analysis is to observe any variations between the response readings for different groups of the input modifications [44]. These disparities are then either attributed to the input variables acting alone (called a single effect) or in combination with another input variable (called an interaction) [44]. If certain input variables or interactions between variables show a remarkable amount of impact on the response readings, the researcher could choose to investigate these input variables or interactions further [44]. Thus, a new DOE project can be drawn up with many more treatments that could allow for a much clearer picture of the effect of these interactions on the response [44].

For this study, the total number of possible input variables (or factors) was established. Then, for each of these factors, the total number of desired treatments (or levels) was determined. It quickly became apparent that the number of experimental runs required for such a study would be around 35,000, and thus require a lifetime of devotion to complete. So, the number of factors and accompanying levels needed to be reduced. It was then determined that the experimental study be split into four smaller, more manageable DOE studies. Each of these manageable DOE studies would focus on certain experimental factors and their effect on the resulting precipitation of Griseofulvin. These factors included the flow rates (and corresponding jet velocity) of the solvent and antisolvent solutions, the angle of impingement of the two jets, the combination of surfactant and/or polymer and their concentration, the sonication power, and the temperature difference between the two feed vessels and main process vessel. Tables **3.1**, **3.2**, **3.3**, and **3.4** below summarizes the number of levels for each factor.

Sonication Power	Angle of Jet Impingement				
	120°		180°		
	Surfactant		Surfactant		
		Tween [®]		Tween®	
	None	80	None	80	
0 W					
125 W					

Table 3.1 The factors and their accompanying levels for the submerged impinging jet DOE #1 investigation (effect of angle of impingement, sonication, & surfactant).

Table 3.2 The factors and their accompanying levels for the submerged impinging jet DOE #2 investigation (effect of difference in temperature between streams).

	Angle of	
	Impingement $= 120^{\circ}$	
	Tween [®] 80	
Sonication	$\Delta T =$	$\Delta T =$
Power	12°C	28°C
0 W		
125 W		

Table 3.3 The factors and their accompanying levels for the submerged impinging jet DOE #3 investigation (effect of surfactant type & sonication power intensity.

	Jet Velocity=2.66 m/s	
Sonication	Tween®	
Power	80	HPMC/SDS
0 W		
75 W		
125 W		
200 W		
250 W		

Sonication	Drug:HPMC:SDS Mass Ratio		
Power	5:1:1	3:1:1	
0 W			
75 W			
125 W			
200 W			
250 W			

Table 3.4 The factors and their accompanying levels for the submerged impinging jet DOE #4 investigation (effect of drug:hpmc:sds mass ratio).

The jet velocity ranged from 2.66 m/s to 15 m/s, while the angle of impingement of the two jets only covered 120° and 180° between the two jet nozzles (as shown in Figure 3.7). The surfactants and polymers used in this study were polysorbate 80 (Tween[®] 80), sodium dodecyl sulfate (SDS), and hydroxypropyl methylcellulose SDS and HPMC were used in combination during experiments, as (HPMC). recommended by Dr. Somenath Mitra and his doctoral student Xiangxin Meng of the Department of Chemistry and Environmental Science at NJIT. Experiments were run without the presence of a surfactant or polymer. This contributed to the first level of this factor. The concentrations for the experimental runs with Tween[®] 80 were 0.0125 mM (0.015 mL/L), which is the critical micelle concentration in water [45]. The concentrations for the experimental runs with SDS and HPMC were 0.23 mg/mL, which was also recommended by Dr. Mitra and Xiangxin Meng. The preparation of the antisolvent solutions was described in Section 3.2.4.2. The sonication power ranged from 0 to 125 W for the Micro-Tip, and 0 to 250 W for the 0.5 in (12.7 mm) diameter tip. The difference in temperature of the two jet streams, ΔT , was either 12°C or 28°C. This covered the treatments that time would allow in order to accomplish a comprehensive investigation of the apparatus.



Figure 3.7 Schematic of two different angles of impingement investigated.

3.2.4 Experimental Procedure

3.2.4.1 Preparation of Drug Solution (Solution A)

A weighed amount of Griseofulvin (usually 8.4 g of drug for 200 mL of acetone or 10.5 g of drug for 250 mL of acetone) was transferred to a volumetric flask and the required volume of acetone was added to it. The flask was then placed in a sonication bath to dissolve the drug in acetone (typically 1 hour). The drug solution was stored at room temperature. The resulting concentration of Griseofulvin in acetone was 42 g/L. This solution was used as a feed solution in all experiments.

3.2.4.2 Preparation of Antisolvent Solution (Solution B)

3.2.4.2.1 Antisolvent Solution Including Tween 80

4000 mL of distilled water was placed in a 4-L volumetric cylinder. A measured amount of Tween 80 (18.8 mL) was added and solution was stirred using magnetic stirrer for 15 minutes. This solution was used as stock solution and stored in the same volumetric cylinder by closing its mouth. The final concentration of Tween 80 in the solution was 0.47 % V/V.

3.2.4.2.2 Antisolvent Solution Including HPMC/SDS

A stock solution was prepared by transferring 700 mL of distilled/de-ionized water to a 2-L Erlenmeyer flask, and then heating and stirring the flask with a magnetic stirrer on a hotplate (Jenway 1000, Essex, UK) until the temperature reached 75°C. Then, 1.5 g of HPMC was added while stirring. After 5 minutes, heating was stopped and 700 mL of distilled/de-ionized water was added. When the solution was sufficiently cooled (50°C), 1.5 g of SDS was added. Stirring was continued for 5 minutes, and then 600 mL of distilled/de-ionized water was added to make 2 Liter of a stock solution. The concentrations of HPMC and SDS in the final solution were both 0.075%W/V. The solution was capped and stored in the same Erlenmeyer flask at room temperature until needed.

3.2.4.3 Impinging Jet Crystallization Process

The anti-solvent reservoir was filled with 1 L of the anti-solvent solution. The water bath for the anti-solvent reservoir was switched on and run for at least 1 hour before the experiments started so that the anti-solvent temperature was low enough (4°C) for the experiment.

After checking the alignment of the jets (visually with a protractor) so that they would point to each other at the desired angle of impingement, the jet assembly was placed in the receiving tank, which had been previously cooled to 4°C by passing the coolant through the jacket. The flow rate of both jets had been adjusted prior to the experiment by passing acetone or water through the jets until the desired impinging jet velocity was adjusted using the flow meters. During this operation, a barrier was placed between the jets so that they would not be contaminated with the other jet's solvent. The impinging velocity was the same (2.66 m/s or 15 m/s) for both jets, but their flow rate was different since the ID of the anti-solvent jet was twice as big as that of the drug solution jet. The sonication probe was placed in between the jets. Depending on the experiment, the receiving tank was initially partially filled with a measured amount of cooled anti-solvent solution so that the jets would not be submerged before experiments started in order to reduce the possibility of jet clogging. In this case, the anti-solvent solution was placed in a 1-L beaker and kept in the circulatory bath and cooled down around 4°C.

When the anti-solvent solution was sufficiently cooled, the drug solution was placed in its reservoir tank (150 mL of drug solution when the larger tank was used, and 100 mL when the smaller tank was used) and both the drug solution and the anti-solvent solution were forced to pass through the jets by turning on the gear pumps simultaneously. Measured amount of anti-solvent solution was added to submerge the jets and at this time the sonicator and the main impeller (in the larger tank only) were switched on at specific rate as soon as jets were submerged (impeller speed was kept constant at 300 RPM in all the experiments). This is performed very quickly, and only takes few seconds to turn on the pumps, then impeller motor and sonicator. Pumps were stopped as soon as drug solution ran out. A typical experiment ran between 5 and 10 minutes depending on the flow rates used.

3.2.5 Characterization Methods

3.2.5.1 Sample Collection

Samples containing suspended crystals from the precipitation process were collected in 50 mL centrifuge tubes from the valve at the bottom of the main process vessel. For some experiments, samples were collected from the upper portion of the tank as well. However, after further study, it was determined that the results from both sampling methods were identical.

3.2.5.2 Laser Diffraction Particle Size Analysis (Beckman-Coulter LS230)

Laser diffraction particle characterization methods have been widely used for particle sizing in many different applications [46]. There are three major advantages of this technique: it can be applied to various kinds of particulate systems, it can be automated, and a variety of commercial instruments with some advanced features are available [46]. However, results can be heavily affected if proper use of the instrument and proper interpretation of the data is not followed.

Laser diffraction technique is based on the measurement scattering angles [46]. The various operating modes for the apparatus are: Fraunhofer diffraction, (near) forward light scattering, and low-angle laser light scattering (LALLS) [46]. However, the technique has been expanded to include a wider angular range for light scattering and apply Mie theory in the analysis [46].

The manner in which particles scatter light is the basis of laser diffraction. When particles scatter light, an intensity pattern that is dependent on particle size is emitted in all directions [46]. The entire incident beam is not always merely scattered, as it is also partially absorbed by the particle [46]. The diffracted light is sent into a very small angle
centered about the forward direction of the incident beam [46]. The form of the angular patterns of scattered intensity depends strongly on the ratio of particle size to wavelength of the beam [46]. However, it should be noted that current laser diffraction instruments assume that all particles are spherically shaped [46]. Thus, a relative particle size is calculated, and the Mie theory predicts the angular pattern of scattered intensity for any value of this relative particle size [46]. The form of this angular pattern is heavily influenced by the relative refractive index [46]. This is the ratio of the refractive index of the particle to that of the medium surrounding the particle [46]. An optical model is used by the computer to analyze scattering patterns for unit volumes of particles in selected size classes [46]. Then, a mathematical procedure is used to calculate a volumetric particle size distribution that fits best with the measured scattering pattern [46].



Figure 3.8 Principles of laser diffraction particle size analysis as performed by the Beckman-Coulter LS230 [46].

A typical laser diffraction instrument consists of a laser source, a particulate dispersion device, a collection lens, a series of detectors for measuring the scattering pattern, and a computer for both control of the instrument and calculation of the particle size distribution [46]. Unfortunately, the laser diffraction technique cannot distinguish between scattering by single particles and scattering by clusters of agglomerated primary particles [46]. In the past, commercial instruments only used scattering angles smaller than 14 degrees, which limited the instrument's ability to measure smaller particle sizes [46]. Since smaller particles show most of their distinctive scattering at larger angles, these instruments were limited to measuring about 1 micron as the lowest possible size [46]. In recent years, instruments began allowing measurement at larger scattering angles, some up to about 150 degrees [46]. The instruments accomplished this either through use of a converging beam, more or larger lenses, a second laser beam, or more detectors [46]. Thus, smaller particles down to about 0.1 micron could be sized [46]. Some instruments even look to improve the characterization of particle sizes in the submicron range by incorporating additional information from scattering intensities and intensity differences at various wavelengths and polarization planes [46].

The laser diffraction instrumenet used in this study, Beckman-Coulter LS230 (Beckman Coulter, Inc., Fullerton, CA, USA) was operated using aqueous suspensions with its wet module. The LS230 has a significant dynamic operating range between 0.04 micron to 2000 micron. The LS230 uses Polarization Intensity Differential Scattering (PIDS) method to measure particles smaller than 0.4 micron. The PIDS system uses incandescent tungsten-halogen lamp and three sets of vertically and horizontally polarized filters to provide monochromic light at three wavelengths: 450 nm (blue), 600 nm (orange), and 900 nm (near-infrared). Measurement is made by analysis of the pattern of the difference in scattering vertically and horizontally polarized light.



Figure 3.9 Beckman-Coulter LS230 located in the W.M. Keck Foundation Laboratory in the Otto York Center for Environmental Engineering and Science Building at NJIT.

3.2.5.3 Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) is a technique that provides the observation and characterization of heterogeneous organic and inorganic materials on a nanometer to micrometer scale [47]. SEM is readily used by a variety of industries due to its ability to obtain three-dimensional-like images of the surface of a wide range of materials [47]. Typically, the most commonly used feature of SEM is to provide topographical images of various solid materials in the magnification range of 10-10,000 X, but the technique is much more versatile and offers more to the user [47]. A high resolution on the order of 1-5 nm (10-50 Angstroms) can be accomplished in the most recent commercial models.



Figure 3.10 The two major parts of the SEM, the electron column (left) and the electronics console (right) [47].

The basic components of a scanning electron microscope include the electron lens system, the electron gun, the electron collector, the visual and photorecording cathode ray tubes (CRTs), and the associated electronics [47]. In a SEM, the area which is to be analyzed (also known as a microvolume) is irradiated by a finely focused electron beam [47]. The electron beam is produced by the electron gun generating electrons and accelerating them to energy in the range 0.1-30 keV (100-30,000 electron volts) [47]. The spot size from the gun is too large to produce a sharp image, thus a series of electron lenses are used to demagnify the beam and finely focus it to the region of interest (Figure 3.11) [47].



Figure 3.11 Schematic of the electron column showing the electron gun, lenses, the deflection system, and the electron detector [47].

The interaction of the electron beam and the sample generates a variety of signals such as secondary electrons, backscattered electrons, characteristic x-rays, and other photons of various energies [47]. These signals are then gathered by the electron collector and analyzed to determine many characteristics of the sample, such as surface topography, crystallography, composition, and more [47]. Secondary and backscattered electrons hold the greatest interest out of the signals produced due to the way they vary as a result of differences in surface topography [47]. The secondary electron emission allows for a resolution approximating the size of the focused electron beam [47]. This results in much crisper, clearer images at a higher magnification [47]. The secondary and backscattering electron signals combine to offer the large depth of field of the SEM, which results in the three-dimensional appearance seen in the captured images [47].



Figure 3.12 Diagram of the backscattered and secondary electron collection [47].

A LEO Field Emission Scanning Electron Microscope (FESEM) equipped with an Oxford UTW X-ray detector is used to analyze the impinging jets mixer experimental results. For each experiment conducted, a minimum of two samples were prepared for SEM analysis. The goal of the SEM study of these samples is to confirm the particle size results of the Beckman-Coulter LS230 and observe crystal shape of these particles. Two separate settings were utilized when analyzing each of the samples: secondary electron (SE) images, and backscattered-electron (BE) images.



Figure 3.13 LEO 1530 VP Field Emission Scanning Electron Microscope (FESEM) located in the Otto York Center for Environmental Engineering and Science Building at NJIT.

Initially, the samples were analyzed using the Robinson Backscattered Detector (RBSD), with an accelerating voltage of 20-25 keV, and a working distance of approximately 9 mm. The RBSD is a wide-angle scintillator photomultiplier type of backscattering detector comprised of an arm of scintillation material with a hole through which the electron beam passes (Figure 3.14). During operation, the RBSD is placed into position over the sample. The BE images obtained contain a great deal of compositional information (atomic-number contrast) which dominates the topographic information. Thus the primary feature of the BE image is the distribution of phases of different average atomic number, while the topography of the surface is only a superimposed secondary feature. So the drug particles are easily visible when using the RBSD, resulting in a better understanding of the location of the most interesting particles.



Figure 3.14 Robinson Backscattered Detector (RBSD) [48].

Once enough BE images have been captured, the samples are re-analyzed using SE. This is performed with a much lower accelerating voltage range of 1-2 keV, and a working distance of approximately 3-5 mm. Since the drug particles are organic, a lower accelerating voltage must be utilized in order to prevent damage from occurring to them during SE operation. The SE images compliment the previously taken BE images. This is due to SE images having their compositional information masked by the dominant topographic search for phases of interest. Also, while operating using SE, a higher resolution can be achieved, which results in higher magnification.

3.2.5.4 Determination of Crystallinity by X-Ray Diffraction (XRD)

An X-Ray Diffraction (XRD) apparatus (Philips PW3040 X-Ray Diffractometer) was used to reveal details about the crystallographic structure of the Griseofulvin. XRD is powerful and versatile nondestructive analytical techniques for the identification and quantitative determination of the crystalline solid phases. XRD samples were prepared by filtering the resulting suspension using filter paper (Glass Fiber Filter, 61631, Pall Life Sciences, Ann Arbor, Michigan) and subsequent drying in the desecator.



Figure 3.15 Philips PW3040 X-Ray Diffractometer (XRD) located in Colton Hall at NJIT.

XRD patterns were compared to the reference pattern available for griseofulvin. Unfortunately, only one reference pattern was available and the information within it was very limited. This limited the XRD study to a comparison of peak size and locations between each of the experimental samples.

3.3 Results and Discussion

The Griseofulvin used in this work was manufactured and donated by Johnson & Johnson. The initial material was analyzed and found to have a mean particle size of 13.56 μ m. However, this material had a wide size distribution ranging from around 1 μ m to about 75 μ m. The shape of these particles was very inconsistent, and ranged from larger chunks to thin shavings. The particle size distribution of the original material is shown in Figure 3.16, and the accompanying SEM micrograph is shown in Figure 3.17.



Figure 3.16 Particle size distribution of griseofulvin manufactured and donated by Johnson & Johnson measured with Beckman-Coulter LS230 apparatus.



Figure 3.17 Electron micrographic image of griseofulvin manufactured and donated by Johnson & Johnson measured with the SEM apparatus.

3.3.1 Submerged Impinging Jets vs Non-submerged Impinging Jets

The initial investigation of this study involved comparing the crystallization results from impinging jets operated in air (non-submerged) to those operated while submerged in an antisolvent solution (distilled water). Experiments were conducted using the impinging jets apparatus shown in Figure 3.6, and an angle of impingement of 120° between the two jet nozzles. 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. No sonication was used during the experiments, and the sonicator probe was not part of these experiments. 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 3.18 shows the crystal size distribution for experiments conducted with the impinging jets operated in air. The mean particle size was found to be 183.6 μ m. The d10 particle size was found to be 109.4 μ m, and the d90 particle size was found to be 264.7 μ m. The particle size distribution was comparable in all experimental samples. An SEM micrograph for the experiment is shown in Figure 3.19. The crystals present in the SEM micrographs were elongated and rod-like. These particles appeared to be around the size of the mean particle size, with some slightly smaller and some slightly greater.



Figure 3.18 Particle size distribution of griseofulvin crystals measured with Beckman-Coulter LS230 apparatus. Impinging jets were operated in air.



Figure 3.19 Electron micrographic image of griseofulvin crystals measured with the SEM apparatus. Impinging jets were operated in air.

Figure 3.20 shows the crystal size distribution for experiments conducted with the impinging jets operated submerged in distilled water. The mean particle size was found

to be 176.2 μ m. The d10 particle size was found to be 105.2 μ m, and the d90 particle size was found to be 245.5 μ m. The particle size distribution was comparable in all experimental samples. An SEM micrograph for the experiment is shown in Figure 3.21. The crystals were present in two different shapes in the SEM micrographs. The shape that accounted for the greatest volume was the elongated and rod-like crystals. These particles appeared to be around the size of the mean particle size and greater. The rod-like crystals accounted for the largest particles in the SEM micrographs. The other crystals were less elongated, but slightly wider. These crystals account for the smaller particle sizes found in the SEM micrographs with sizes along the lines of 45-50 μ m.



Figure 3.20 Particle size distribution of griseofulvin crystals measured with Beckman-Coulter LS230 apparatus. Impinging jets were operated submerged in distilled water.



Figure 3.21 Electron micrographic image of griseofulvin crystals measured with the SEM apparatus. Impinging jets were operated submerged in distilled water.

A comparison between the impinging jets experiments operated in air and those submerged in distilled water can be performed by analyzing the particle size distributions and SEM micrographic images. While there is not a significant difference between the mean particle sizes in the two cases, the submerged impinging jets case does produce a smaller mean particle size. Also, the submerged impinging jets case resulted in a slightly tighter particle size distribution. This is most likely due to the larger supply of antisolvent in the submerged case, which would allow for a more rapid, complete precipitation of the griseofulvin. This is very important as control of the crystallization process is desired. The SEM micrographic images confirm the conclusions from the particle size distributions. Thus, it has been determined that the submerged impinging jets produce more desirable results than the impinging jets operated in air. After it was determined that the impinging jets submerged in distilled water produced better results, experiments were conducted in this manner throughout the remainder of the study.

3.3.2 Design of Experiments (DOE) #1 – Effect of Angle of Impingement, Sonication, & Surfactant

The first of the four DOE investigations involved understanding the effect of angle of impingement, presence of sonication, and presence of a surfactant. This was a three factor DOE with each factor having two levels. 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. For the final factor, the antisolvent solution was prepared in two separate ways accounting for the two levels. The first level included only distilled water as the antisolvent solution, and the second level included a mixture of Tween 80 and distilled water as the antisolvent solution prepared as described in Section 3.2.4.2.1. All experiments were conducted using the impinging jets apparatus shown in Figure 3.6. 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.

Table **3.5** and Figure 3.22 summarize the results of the griseofulvin mean particle size in micrometers from the DOE #1 investigation. These results are averages of

replicate experiments run under similar experimental conditions. The individual particle size distributions of each experimental condition investigated in DOE #1 and their accompanying SEM micrographic images can be found in Appendix C (Figures C.2.1-C.2.8).

Table **3.5** and Figure 3.22 show that the presence of sonication in a submerged impinging jets mixing system has the greatest impact on the mean particle size of the precipitated griseofulvin. For example, the mean particle size of griseofulvin dropped from 176.2 μ m with no sonication to 38.23 μ m in the presence of sonication (125 W), a reduction of 78.3%. A significant reduction in mean particle size can also be seen for all experiments in DOE #1 when sonication is present. 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 DOE #1 also show that the impinging jets system produced crystals with smaller mean particle sizes when the two jets were oriented 180° degrees apart and pointed directly at each other. For example, the mean particle size of griseofulvin dropped from $38.23 \mu m$ in the case with 125 W of sonication at an angle of impingement of 120° to $18.68 \mu m$ 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 180° apart maximizes the kinetic energy of the streams, while minimizing the mixing time of the streams. Though this increase in kinetic energy between the 120° angle of impingement and 180° 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 final factor studied was the presence of a surfactant in the anti-solvent solution. Table **3.5** and Figure 3.22 display the effect of Tween® 80 on the mean particle size of griseofulvin for experimental cases involving both angles of impingement and sonication powers. In all experimental cases, Tween® 80 was shown to help reduce the mean particle size of griseofulvin. For example, the mean particle size of griseofulvin dropped from 82.47 μ m in the case without the presence of Tween® 80 at an angle of impingement of 180° to 43.09 μ m in the case with the presence of Tween® 80 at an angle of impingement of 180°, a reduction of 47.8%. This was expected as the presence of Tween® 80 around the griseofulvin crystals is expected to stabilize the crystals within a suspension comprised mostly of water.

	Angle of Impingement of the Jets			
Sonication	120°		180°	
Power	Surfactant		Surfactant	
		Tween®		Tween®
	None	80	None	80
0 W	176.2	47.03	82.47	43.09
125 W	38.23	25.58	18.68	14.98

Table 3.5 DOE #1 mean particle size results of griseofulvin in μm .



Figure 3.22 DOE #1 mean particle size results of griseofulvin in micrometers.

Table **3.6** and Figure 3.23 summarize the results of the griseofulvin d10 particle size in micrometers, and Table **3.7** and Figure 3.24 summarize the results of the griseofulvin d90 particle size in micrometers from the DOE #1 investigation. These results are averages of a minimum of three replicate experiments run under similar experimental conditions.

Tables **3.6** and **3.7**, and Figures 3.23 and 3.24 show that the presence of sonication in a submerged impinging jets mixing system also has a significant effect on the d10 and d90 particle sizes of the precipitated griseofulvin. For example, the d10 particle size of griseofulvin dropped from 105.2 μ m with no sonication to 12.97 μ m in the presence of sonication (125 W), a reduction of 87.7%; and the d90 particle size of griseofulvin dropped from 245.5 μ m with no sonication to 57.02 μ m in the presence of

sonication (125 W), a reduction of 76.8%. A significant reduction in d10 and d90 particle sizes can also be seen for all experiments in DOE #1 when sonication is present. This means that the additional energy delivered to the precipitation zone between the two jet nozzles by the sonicator not only helped to produce smaller mean particle sizes, but also a tighter, smaller particle size distribution.

The results of DOE #1 also show that the impinging jets system produced crystals with smaller d10 and d90 particle sizes when the two jets were oriented 180° degrees apart and pointed directly at each other. For example, the d10 particle size of griseofulvin dropped from 12.97 μ m in the case with 125 W of sonication at an angle of impingement of 120° to 6.191 μ m in the case with 125 W at an angle of impingement of 180°, a reduction of 52.3%; and the d90 particle size of griseofulvin dropped from 57.02 μ m in the case with 125 W of sonication at an angle of 120° to 33.03 μ m in the case with 125 W at an angle of 120° to 33.03 μ m in the case with 125 W at an angle of 120° to 33.03 μ m in the case with 125 W at an angle of impingement of 120° to 33.03 μ m in the case with 125 W at an angle of impingement of 180°, a reduction of 42.1%. This means that maximizing the kinetic energy delivered to the precipitation zone between the two jet nozzles by having the two jet streams colliding with the jet nozzles oriented at 180° apart not only helped to produce smaller mean particle sizes, but also a tighter, smaller particle size distribution.

Tables **3.6** and **3.7**, and Figures 3.23 and 3.24 also display the effect of Tween® 80 on the d10 and d90 particle sizes of griseofulvin for experimental cases involving both angles of impingement and sonication powers. In all experimental cases, Tween® 80 was shown to help reduce the d10 and d90 particle sizes of griseofulvin. For example, the d10 particle size of griseofulvin dropped from 22.97 μ m in the case without the presence of Tween® 80 at an angle of impingement of 180° to 12.31 μ m in the case with

the presence of Tween® 80 at an angle of impingement of 180° , a reduction of 46.4%. Similarly, the d90 particle size of griseofulvin dropped from 156.2 µm in the case without the presence of Tween® 80 at an angle of impingement of 180° to 76.16 µm in the case with the presence of Tween® 80 at an angle of impingement of 180° , a reduction of 51.2%. This means that the presence of Tween® 80 around the griseofulvin crystals helped to produce smaller mean particle sizes, as well as a tighter, smaller particle size distribution.

	Angle of Jet Impingement				
Sociection	120°		180°		
Power	Surfa	Surfactant		Surfactant	
		Tween [®]		Tween [®]	
	None	80	None	80	
0 W	105.2	13.77	22.97	12.31	
125 W	12.97	6.724	6.191	4.777	

Table 3.6 DOE #1 d10 particle size results of griseofulvin in μ m.



Figure 3.23 DOE #1 d10 particle size results of griseofulvin in μ m.

	Angle of Jet Impingement				
Sonication	120°		180°		
Power	Surfactant		Surfa	Surfactant	
		Tween®		Tween®	
	None	80	None	80	
0 W	245.5	85.74	156.2	76.16	
125 W	57.02	37.16	33.03	27.06	

Table 3.7 DOE #1 d90 particle size results of griseofulvin in µm.



Figure 3.24 DOE #1 d90 particle size results of griseofulvin in µm.

The DOE #1 investigation has shown that the impinging jets system produced crystals with smaller mean particle sizes when the two jets were oriented 180 degrees apart and pointed directly at each other than when the two jets were oriented in a 120 degree configuration. Also, the introduction of ultrasonic power at the impingement point resulted in markedly smaller mean particle size and a tighter particle size distribution. The addition of sonication and Tween[®] 80 to the impinging jets experiments helped to reduce the mean particle size from above 100 μ m to below 15 μ m. Thus, it was determined that an angle of impingement of 180 degrees, the presence of sonication, and the presence of a surfactant were important towards the rapid precipitation of griseofulvin.

3.3.3 Design of Experiments (DOE) #2 – Effect of Difference in Temperature between Streams

The second of the four DOE investigations involved understanding the effect of the difference in temperature between the two jet streams. This was a two factor DOE with each factor having two levels. The two temperature differences used were 12°C and 28°C. For the temperature difference of 12°C, the temperature of the solvent solution was maintained around 34°C, while the antisolvent solution was maintained around 22°C. For the temperature difference of 28°C, the temperature of the solvent solution was maintained around 34°C, while the antisolvent solution was maintained at a much cooler 6° C. This accounted for the two levels of this factor. The two levels of sonication was the same as the first DOE investigation. All experiments were conducted using the impinging jets apparatus shown in Figure 3.6. The angle of impingement was maintained at 120° during these experiments. The antisolvent solution included a mixture of Tween 80 and distilled water as the antisolvent solution prepared as described in Section 3.2.4.2.1. 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. For each experiment, the particle size distribution was determined multiple times with the Beckman-Coulter LS230 apparatus, and the results averaged accordingly.

Table **3.8** and Figure 3.25 summarize the results of the griseofulvin mean particle size in micrometers from the DOE #2 investigation. These results are averages of a minimum of three replicate experiments run under similar experimental conditions. The individual particle size distributions of each experimental condition investigated in DOE #2 and their accompanying SEM micrographic images can be found in Appendix C (Figures C.3.1-C.3.4).

Table **3.8** and Figure 3.25 show that the larger of the two temperature differences between the two process streams has the greater impact on the mean particle size of the precipitated griseofulvin. For example, the mean particle size of griseofulvin dropped from 47.03 μ m in the case with a stream temperature difference of 12°C to 33.09 μ m in the case with a stream temperature difference of 28°C, a reduction of 29.6%. A similar reduction in mean particle size can also be seen for all experiments in DOE #2 when the larger stream temperature difference is utilized. This decrease in particle size was expected as the lower temperature enhances supersaturation and promotes nucleation over crystal growth.

The results of DOE #2 also confirmed the findings of DOE #1 with regards to the presence of sonication during crystallization. For example, the mean particle size of griseofulvin dropped from 33.09 μ m in the case with no sonication and the stream temperature difference of 28°C to 9.673 μ m in the case with 125 W of sonication present and the stream temperature difference of 28°C, a reduction of 70.8%. This effect of mean particle size was evident in all experimental cases.







Figure 3.25 DOE #2 mean particle size results of griseofulvin in μ m.

Table **3.9** and Figure 3.26 summarize the results of the griseofulvin d10 particle size in micrometers, and Table **3.10** and Figure 3.27 summarize the results of the griseofulvin d90 particle size in micrometers from the DOE #2 investigation. These results are averages of replicate experiments run under similar experimental conditions.

Tables **3.9** and **3.10**, and Figures 3.26 and 3.27 show that the larger of the two temperature differences between the two process streams has the greater impact on the

d10 and d90 particle sizes of the precipitated griseofulvin. For example, the d10 particle size of griseofulvin dropped from 13.77 μ m in the case with a stream temperature difference of 12°C to 12.93 μ m in the case with a stream temperature difference of 28°C, a reduction of 6.1%; and the d90 particle size of griseofulvin dropped from 85.74 μ m in the case with a stream temperature difference of 12°C to 61.82 μ m in the case with a stream temperature difference of 28°C, a reduction of 27.9%. While this was a lower reduction than in previous cases, additional experiments conducted under sonication also saw a reduction in d10 particle size. Thus, the larger stream temperature difference did promote smaller mean particle sizes and tighter, smaller particle size distributions of griseofulvin.

The results of DOE #2 also confirmed the findings of DOE #1 with regards to the presence of sonication during crystallization. For example, the d10 particle size of griseofulvin dropped from 12.93 μ m in the case with no sonication and the stream temperature difference of 28°C to 3.348 μ m in the case with 125 W of sonication present and the stream temperature difference of 28°C, a reduction of 74.1%; and the d90 particle size of griseofulvin dropped from 61.82 μ m in the case with no sonication and the stream temperature difference of 28°C to 17.66 μ m in the case with 125 W of sonication present and the stream temperature difference of 28°C to 17.66 μ m in the case with 125 W of sonication present and the stream temperature difference of 28°C, a reduction of 71.4%. This effect of d10 and d90 particle sizes was evident in all experimental cases.



Table 3.9 DOE #2 d10 particle size results of griseofulvin in μ m.



Figure 3.26 DOE #2 d10 particle size results of griseofulvin in μ m.

	Angle of		
	Impingement = 120°		
	Tween [®] 80		
Sonication	$\Delta T =$	$\Delta T =$	
Power	12°C	28°C	
0 W	85.74	61.82	
125 W	37.16	17.66	

Table 3.10 DOE #2 d90 particle size results of griseofulvin in μ m.



Figure 3.27 DOE #2 d90 particle size results of griseofulvin in μ m.

The DOE #2 investigation has shown that the impinging jets system produced crystals with smaller mean particle sizes when a large temperature difference was introduced between the two process streams. The control of experimental temperature helped to enhance supersaturation and provide a tighter particle size distribution. Also, this investigation confirmed the conclusion of DOE #1 in that the addition of sonication to the process resulted in markedly smaller mean particle size and a tighter particle size distribution. Thus, it was determined that the experimental temperature should be carefully controlled, and a large temperature difference between the solvent and antisolvent streams was desired.

3.3.4 Single Solvent Jet vs Two Impinging Jets

Another important investigation of this study involved comparing the crystallization results from experiments operated with a single submerged jet stream (solvent solution) and operated with two submerged jet streams (solvent and antisolvent solutions). Experiments were conducted using the impinging jets apparatus shown in Figure 3.6. For the single jet stream experiments, the antisolvent jet was not operated and thus there was no measurable angle of impingement. For the two submerged impinging jets experiments, an angle of impingement of 180° between the two jet nozzles was used since DOE #1 concluded this configuration was ideal. 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. A sonication power of 125 W and a mixture of Tween 80 and distilled water as the antisolvent solution, prepared as described in Section 3.2.4.2.1, was utilized during these experiments. During each experiment, the temperature of the solvent solution was maintained around 34°C, while the antisolvent solution was maintained at a much cooler 6°C for a temperature difference of 28°C. For each experiment, the particle size distribution was determined multiple times with the Beckman-Coulter LS230 apparatus, and the results averaged accordingly.

Figure 3.28 shows the crystal size distribution for experiments conducted with the single submerged jet. The mean particle size was found to be 32.24 μ m. The d10 particle size was found to be 12.38 μ m, and the d90 particle size was found to be 55.30 μ m. The particle size distribution was comparable in all experimental samples. An SEM micrograph for the experiment is shown in Figure 3.29. The crystals present in the SEM

micrographs were elongated and needle-like. The majority of the particles that appeared in the SEM micrographs were around the size of the mean particle size.



Figure 3.28 Particle size distribution of griseofulvin crystals measured with Beckman-Coulter LS230 apparatus. Single solvent jet stream was operated submerged in antisolvent solution while undergoing 125 W of sonication.



Figure 3.29 Electron micrographic image of griseofulvin crystals measured with the SEM apparatus. Single solvent jet stream was operated submerged in antisolvent solution while undergoing 125 W of sonication.

Figure 3.30 shows the crystal size distribution for experiments conducted with the single submerged jet. The mean particle size was found to be 9.673 μ m. The d10 particle size was found to be 3.348 μ m, and the d90 particle size was found to be 17.66 μ m. The particle size distribution was comparable in all experimental samples. An SEM micrograph for the experiment is shown in Figure 3.31. The crystals present in the SEM micrographs were consistently tetragonal bipyramidal in shape. The majority of the particles that appeared in the SEM micrographs were around the size of the mean particle size.



Figure 3.30 Particle size distribution of griseofulvin crystals measured with Beckman-Coulter LS230 apparatus. Two impinging jets were operated submerged in antisolvent solution while undergoing 125 W of sonication.



Figure 3.31 Electron micrographic image of griseofulvin crystals measured with the SEM apparatus. Two impinging jets were operated submerged in antisolvent solution while undergoing 125 W of sonication.

The results of this investigation clearly display that the experiments operated with a single submerged solvent jet stream failed to meet the performance of the two submerged impinging jets system. The two submerged impinging jets system surpassed the single submerged jet system with both a smaller mean particle size and a tighter particle size distribution. Another advantage of the two submerged impinging jets system is the consistent production of the more desirable tetragonal bipyradmidal particles. Thus, as a result of this investigation, it was determined that the two submerged impinging jets system should continue to be utilized, while the single submerged jet study was ceased.

3.3.5 Design of Experiments (DOE) #3 – Effect of Surfactant Type & Sonication Power Intensity

The third of the four DOE investigations involved understanding the effect of the surfactant mixed into the antisolvent solution and the sonication power intensity. This was a two factor DOE study. The surfactant type factor included two levels. The first level had the antisolvent solution comprised of a mixture of Tween 80 and distilled water and prepared as described in Section 3.2.4.2.1. The second level had the antisolvent solution comprised of a mixture of HPMC, SDS, and distilled water and prepared as described in Section 3.2.4.2.2. 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 3.3. The two temperature differences used were 12°C and 28°C. A temperature difference between the two jet streams of 28°C, the angle of impingement of 180°, 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.

Table **3.11** and Figure 3.32 summarize the results of the griseofulvin mean particle size in micrometers from the DOE #3 investigation. These results are averages of replicate experiments run under similar experimental conditions. The individual particle size distributions of each experimental condition investigated in DOE #3 and their accompanying SEM micrographic images can be found in Appendix C (Figures C.4.1-C.4.10).

	Jet Velocity=2.66 m/s		
Sonication	Tween [®]		
Power	80	HPMC/SDS	
0 W	39.83	32.68	
75 W	8.141	4.715	
125 W	6.144	3.92	
200 W	7.328	2.355	
250 W	6.664	2.415	

Table 3.11 DOE #3 mean particle size results of griseofulvin in µm.



Figure 3.32 DOE #3 mean particle size results of griseofulvin in μ m.

In addition to Table **3.11** and Figure 3.32, the data for the mean particle size were subjected to a two-way ANOVA (analysis of variance) with the following mathematical model:

$$Y_{ijk} = \mu + P_i + S_{j} + PS_{ij} + \varepsilon_{k(ij)}$$
(14)

Where P is sonication power treatment,

S is surfactant choice,

i = 1, 2, 3, 4, 5 for the five levels of sonication power

j = 1, 2 for the two values of surfactant

 \mathbf{k} = for the number of observations in each i, j treatment combination

 $\varepsilon_{k(ij)}$ = the error within each of the treatment combinations.

The ANOVA summary can be found in Table 3.12. According to the ANOVA results,

the sonication power intensity and the type of surfactant are both statistically significant

at the 99% confidence level.

	df	F	p	
			1.36E-	
Power (P)	4	608.8353918	43	significant
Surfactant			6.87E-	
(S)	1	562.4276255	30	significant
PxS	4	0		
error	53			
total	62			

 Table 3.12
 Summary of two-way ANOVA for DOE #3 mean particle size investigation.

Table **3.13** and Figure 3.33 summarize the results of the griseofulvin d10 particle size in micrometers, and Table **3.15** and Figure 3.34 summarize the results of the griseofulvin d90 particle size in micrometers from the DOE #3 investigation. These results are averages of replicate experiments run under similar experimental conditions.

	Jet Velocity=2.66 m/s		
Sonication	Tween [®]		
Power	80	HPMC/SDS	
0 W	12.02	7.898	
75 W	2.114	2.4145	
125 W	2.100	1.8181	
200 W	2.407	1.2610	
250 W	2.409	1.2400	

Table 3.13 DOE #3 d10 particle size results of griseofulvin in μ m.



Figure 3.33 DOE #3 d10 particle size results of griseofulvin in µm.

In addition to Table **3.13** and Figure 3.33, the data for the d10 particle size were subjected to a two-way ANOVA (analysis of variance) with the same mathematical model found in Equation 14.

The ANOVA summary can be found in Table **3.14**. According to the ANOVA results, the sonication power intensity and the type of surfactant are both statistically significant on 99% confidence level.

	df	F	р	
			4.06E-	
Power (P)	4	43.39182487	16	significant
Surfactant			2.03E-	
(S)	1	52.06058008	09	significant
PxS	4	0		
error	53			
total	62			

Table 3.14 Summary of two-way ANOVA for DOE #3 d10 particle size investigation.

Table 3.15 DOE #3 d90 particle size results of griseofulvin in μ m.

	Jet Velocity=2.66 m/s		
Sonication	Tween®		
Power	80	HPMC/SDS	
0 W	68.60	54.756	
75 W	16.56	7.4060	
125 W	11.41	6.1460	
200 W	13.12	3.8150	
250 W	11.84	4.0375	


Figure 3.34 DOE #3 d90 particle size results of griseofulvin in µm.

In addition to Table **3.15** and Figure 3.34, the data for the d90 particle size were subjected to a two-way ANOVA (analysis of variance) with the same mathematical model found in Equation 14.

The ANOVA summary can be found in Table **3.16**. According to the ANOVA results, the sonication power intensity and the type of surfactant are both statistically significant on 99% confidence level.

	df	F	р	
			1.91E-	
Power (P)	4	1729.657744	55	significant
Surfactant			1.35E-	
(S)	1	2153.239895	44	significant
PxS	4	0		
error	53			
total	62			

 Table 3.16
 Summary of two-way ANOVA for DOE #3 d90 particle size investigation.

The DOE #3 investigation has shown that the impinging jets system produced crystals with smaller mean particle sizes when a combination of HPMC and SDS was mixed with the antisolvent solution than when the Tween 80 mixture was used. The HPMC and SDS mixture experiments showed smaller mean particle sizes and tighter. smaller particle size distributions for all sonication power intensities investigated. The combination of HPMC and SDS helped to stabilize the griseofulvin in the mostly waterbased 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. Such asymptotic values of the particle size were only partially affected by the surfactant used, with mean asymptotic particles sizes on the order of 2-4 µm for the HPMC and SDS combination and 6-8 µm for the Tween 80 mixture. A two-way ANOVA statistical mathematical model showed that the sonication power intensity and the type of surfactant are both statistically significant for the mean, d10, and d90 particle sizes on 99% confidence level. 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.

3.3.6 Design of Experiments (DOE) #4 – Effect of Drug:HPMC:SDS Mass Ratio

The fourth of the four DOE investigations involved understanding the effect of the mass ratio between griseofulvin, HPMC, and SDS on the final crystal shape and size. This was a two-factor DOE study. Two different griseofulvin:HPMC:SDS mass ratios were used in this study, i.e, 5:1:1, and 3:1:1. 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 3.3. A temperature difference between the two jet streams of 28°C, the angle of impingement of 180°, and the solvent flow rate and jet velocity were kept constant at 182.4 mL/min and 15 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.

Table **3.17** and Figure 3.35 summarize the results of the griseofulvin mean particle size in micrometers from the DOE #4 investigation. These results are averages of replicate experiments run under similar experimental conditions. The individual particle size distributions of each experimental condition investigated in DOE #4 and their accompanying SEM micrographic images can be found in Appendix C (Figures C.5.1-C.5.10).

Sonication	Drug:HPMC:SDS Mass Ratio		
Power	5:1:1	3:1:1	
0 W	28.97	32.68	
75 W	7.287	4.715	
125 W	4.475	3.92	
200 W	4.668	2.355	
250 W	5.224	2.415	

Table 3.17 DOE #4 mean particle size results of griseofulvin in μ m.



Figure 3.35 DOE #4 mean particle size results of griseofulvin in μ m.

In addition to Table **3.17** and Figure 3.35, the data for the mean particle size were subjected to a two-way ANOVA (analysis of variance) with the following mathematical model:

$$Y_{ijk} = \mu + P_i + R_j + PR_{ij} + \varepsilon_{k(ij)}$$
(15)

Where P is sonication power treatment,

R is drug-to-HPMC-to-SDS mass ratio,

i = 1, 2, 3, 4, 5 for the five levels of sonication power

j = 1, 2 for the two values of mass ratio

 \mathbf{k} = for the number of observations in each i, j treatment combination

 $\varepsilon_{k(ij)}$ = the error within each of the treatment combinations.

The ANOVA summary can be found in Table 3.18. According to the ANOVA results,

the sonication power intensity is statistically significant on 99% confidence level, but the

drug-to-HPMC-to-SDS mass ratio is not statistically significant.

 Table 3.18
 Summary of two-way ANOVA for DOE #4 mean particle size investigation.

	df	F	р	
Power				
<u>(P)</u>	4	125.9285	6.19823E-51	significant
Ratio (R)	1	1.809422	0.180279229	not significant
PxR	4	2.085155	0.084609758	not significant
error	179			
total	188			

Table **3.19** and Figure 3.36 summarize the results of the griseofulvin d10 particle size in micrometers, and Table **3.21** and Figure 3.37 summarize the results of the griseofulvin d90 particle size in micrometers from the DOE #4 investigation. These results are averages of replicate experiments run under similar experimental conditions.

Sonication	Drug:HPMC:SDS Mass Ratio		
Power	5:1:1	3:1:1	
0 W	10.36	7.898	
75 W	2.248	2.415	
125 W	1.707	1.818	
200 W	1.742	1.261	
250 W	1.778	1.240	

Table 3.19 DOE #4 d10 particle size results of griseofulvin in μm.



Figure 3.36 DOE #4 d10 particle size results of griseofulvin in µm.

In addition to Table **3.19** and Figure 3.36, the data for the d10 particle size were subjected to a two-way ANOVA (analysis of variance) with the same mathematical model found in Equation 15.

The ANOVA summary can be found in Table **3.20**. According to the ANOVA results, the sonication power intensity, the drug-to-HPMC-to-SDS mass ratio, and the interaction between the two are statistically significant on 99% confidence level.

	df	F	р	
Power				
(P)	4	312.2542	1.51666E - 79	significant
Ratio (R)	1	12.31152	0.000569362	significant
PxR	4	10.43582	1.27606E-07	significant
error	179			
total	188			

 Table 3.20
 Summary of two-way ANOVA for DOE #4 d10 particle size investigation.

Table 3.21 DOE #4 d90 particle size results of griseofulvin in μ m.

Sonication	Drug:HPMC:SDS Mass Ratio		
Power	5:1:1	3:1:1	
0 W	51.65	54.76	
75 W	14.90	7.406	
125 W	7.654	6.146	
200 W	9.533	3.815	
250 W	10.97	4.038	



Figure 3.37 DOE #4 d90 particle size results of griseofulvin in µm.

In addition to Table **3.21** and Figure 3.37, the data for the d90 particle size were subjected to a two-way ANOVA (analysis of variance) with the same mathematical model found in Equation 15.

The ANOVA summary can be found in Table **3.22**. According to the ANOVA results, the sonication power intensity is statistically significant on 99% confidence level, but the drug-to-HPMC-to-SDS mass ratio is not statistically significant.

	df	F	р	
Power				
(P)	4	113.4231	5.46663E-48	significant
				not
Ratio (R)	1	4.53802	0.034515668	significant
				not
PxR	4	1.989566	0.098021456	significant
error	179			
total	188			

 Table 3.22
 Summary of two-way ANOVA for DOE #4 d90 particle size investigation.

The DOE #4 investigation has shown that the impinging jets system produced crystals with slightly smaller mean particle sizes when the amount of HPMC and SDS was increased in the experimental procedure. However, the two-way ANOVA statistical mathematical model found that the amount of HPMC and SDS relative to the amount of griseofulvin present was not statistically significant with regards to mean and d90 particle sizes on 99% confidence level when comparing the two levels investigated in this study. The model did find that it was statistically significantly with regards to d10 particle sizes on 99% confidence level. Thus, the amount of HPMC and SDS has a greater effect on the particle size distribution than the actual mean particle size. DOE #4 also confirmed the findings of the DOE #3 study regarding the performance of sonication power intensity on the precipitation of griseofulvin. The two-way ANOVA statistical mathematical model of DOE #4 showed the same conclusion regarding sonication power intensity as the two-way ANOVA model of DOE #3.

3.3.7 Effect of Jet Velocity

Another important investigation of this study involved the investigation of the effect of the fluid jet velocity on the crystallization of griseofulvin. Two separate solvent jet velocities were investigated. For the lower jet velocity, the solvent flow rate and jet velocity were kept constant at 32.3 mL/min and 2.66 m/s respectively. For the higher jet velocity, the solvent flow rate and jets velocity were maintained at 182.4 mL/min and 15 m/s respectively. Experiments were conducted using the impinging jets apparatus shown in Figure 3.3. An angle of impingement of 180° between the two jet nozzles was used for both cases. No sonication power was applied. A mixture of HPMC, SDS, and distilled water as the antisolvent solution, prepared as described in Section 3.2.4.2.2, was utilized in these experiments. During each experiment, the temperature of the solvent solution was maintained around 34°C, while the antisolvent solution was maintained at a much cooler 6°C for a temperature difference of 28°C. For each experiment, the particle size distribution was determined multiple times with the Beckman-Coulter LS230 apparatus, and the results averaged accordingly.

Figure 3.38 shows the crystal size distribution for experiments conducted with the lower solvent jet velocity (2.66 m/s). The mean particle size was found to be 32.68 μ m. The d10 particle size was found to be 7.898 μ m, and the d90 particle size was found to be 54.76 μ m. The particle size distribution was comparable in all experimental samples. An SEM micrograph for the experiment is shown in Figure 3.39. The crystals present in the SEM micrographs were elongated and rod-like, and often were loosely joined in clusters or agglomerates as seen in the image. The particles that appeared in the SEM

micrographs fell within the size range displayed in the particle size distribution. However, the majority were around the size of the mean particle size.



Figure 3.38 Particle size distribution of griseofulvin crystals measured with Beckman-Coulter LS230 apparatus. Lower solvent jet velocity (2.66 m/s) was operated submerged in antisolvent solution with no sonication.



Figure 3.39 Electron micrographic image of griseofulvin crystals measured with the SEM apparatus. Lower solvent jet velocity (2.66 m/s) was operated submerged in antisolvent solution with no sonication.

Figure 3.40 shows the crystal size distribution for experiments conducted with the higher solvent jet velocity (15 m/s). The mean particle size was found to be 28.97 μ m. The d10 particle size was found to be 10.36 μ m, and the d90 particle size was found to be 51.65 μ m. The particle size distribution was comparable in all experimental samples. An SEM micrograph for the experiment is shown in Figure 3.41. The crystals present in the SEM micrographs were elongated and rod-like in shape. The particles were generally seen agglomerated in the SEM images. The particles that appeared in the SEM micrographs fell within the size range displayed in the particle size distribution. However, the majority were around the size of the mean particle size.



Figure 3.40 Particle size distribution of griseofulvin crystals measured with Beckman-Coulter LS230 apparatus. Higher solvent jet velocity (15 m/s) was operated submerged in antisolvent solution with no sonication.



Figure 3.41 Electron micrographic image of griseofulvin crystals measured with the SEM apparatus. Higher solvent jet velocity (15 m/s) was operated submerged in antisolvent solution with no sonication.

The results of this investigation display that the experiments operated with a higher solvent jet velocity produced a slightly smaller mean particle size than the lower solvent jet velocity experiments. The d10 and d90 particle sizes were found to be in close proximity, but a visual observation of the particle size distributions and SEM micrographs showed that the higher jet velocity experiments produced a greater amount of smaller sized particles. The higher jet velocity experiments introduced more kinetic energy to the point of impingement, and were expected to form smaller particles. However, a more significant study involving a range of solvent jet velocities should be conducted to better understand how this variable effects both the mean particle size and particle size distribution. For now, it can only be concluded that the higher jet velocity does offer an advantage over the lower jet velocity, but it is not known if this advantage

is significant enough to warrant the higher equipment and materials cost associated with achieving this higher jet velocity, especially when sonication offers a much higher amount of energy.

3.3.8 X-Ray Diffraction Analysis

A comparison was made between the XRD spectra obtained under different experimental Figures 3.42 and 3.43 show the XRD data from samples obtained in conditions. experiments with Tween 80 as the surfactant and with HPMC and SDS as the stabilizing mixture, respectively. The results presented in Figure 3.42 show that very similar spectra for griseofulvin were obtained irrespective of the operating conditions used in the experiments. This indicates that the crystal habit of griseofulvin was the same irrespective of the experimental conditions. The results of that figure can be compared with those of Figure 3.43. This figure also shows the spectrum for unprocessed Griseofulvin as a reference (top panel), and those for pure HPMC and SDS (second and third panel). All the Griseofulvin spectra in Figures 3.42 and 3.43 appear identical to each other irrespective of the sonication power and jet velocity, indicating that the same Griseofulvin crystal structure was formed. These spectra do not overlap with the HPMC and SDS spectra, which were therefore not incorporated in the Griseofulvin particles, confirming that the crystals were just made of Griseofulvin in all cases.



Figure 3.42 XRD Data for the Tween 80 as the surfactant cases.



Figure 3.43 XRD Data for the combination of HPMC and SDS as the stabilizing mixture.

3.4 Conclusions for this Chapter

A comparison between the results with the impinging jets experiments operated in air and those obtained with submerged jets in distilled water can be performed by analyzing the particle size distributions and SEM micrographic images. While the difference between the mean particle sizes in the two cases is limited, the submerged impinging jets case does deliver a smaller mean particle size. Also, the submerged impinging jets case delivered a slightly tighter particle size distribution. This is most likely due to the larger supply of antisolvent in the submerged case, which would allow for a more rapid, complete precipitation of the griseofulvin. This is an important aspect, as a tighter control of the crystallization process is always desired. The SEM micrographic images confirm the conclusions reached by examining the particle size distributions. Thus, it can be concluded that the submerged impinging jets produce more desirable results than the impinging jets operated in air.

The DOE #1 investigation has shown that the impinging jets system produced crystals with smaller mean particle sizes when the two jets were oriented 180 degrees apart and pointed directly at each other than when the two jets were oriented in a 120 degree configuration. More significantly, the introduction of ultrasonic power at the impingement point resulted in markedly smaller mean particle size and a tighter particle size distribution. The addition of sonication and presence of Tween[®] 80 to the impinging jets experiments helped to reduce the mean particle size from above 100 μ m to below 15 μ m. Thus, it was determined that an angle of impingement of 180 degrees, the presence of sonication, and the presence of a surfactant were important towards the rapid precipitation of griseofulvin.

The DOE #2 investigation has shown that the impinging jets system produced crystals with smaller mean particle sizes when a large temperature difference was introduced between the two process streams. The control of the experimental temperature helped to enhance supersaturation and provide a tighter particle size distribution. Also, this investigation confirmed the conclusion of DOE #1 in that the addition of sonication to the process resulted in markedly smaller mean particle size and a tighter particle size distribution. Thus, it was concluded that the experimental temperature should be carefully controlled, and a large temperature difference between the solvent and antisolvent streams is desired.

A comparison of the results of the single jet stream experiments with those of the two jet streams investigation clearly shows that the experiments operated with a single submerged solvent jet stream failed to meet the performance of the two submerged impinging jets system. The two submerged impinging jets system surpassed the single submerged jet system with both a smaller mean particle size and a tighter particle size distribution. Another advantage of the two submerged impinging jets system is the consistent production of the more desirable tetragonal bipyradmidal particles. Thus, the two submerged impinging jets system should be preferentially utilized, and no additional work was conducted with the single submerged jet.

The DOE #3 investigation has shown that the impinging jets system produced crystals with smaller mean particle sizes when a combination of HPMC and SDS was mixed with the antisolvent solution than when the Tween 80 mixture was used. The HPMC and SDS mixture experiments showed smaller mean particle sizes and tighter, smaller particle size distributions for all sonication power intensities investigated. The combination of HPMC and SDS helped to stabilize the griseofulvin in the mostly waterbased 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. Such asymptotic values of the particle size were only partially affected by the surfactant used, with mean asymptotic particles sizes on the order of 2-4 μ m for the HPMC and SDS combination and 6-8 μ m for the Tween 80 mixture. A two-way ANOVA statistical mathematical model showed that the sonication power intensity and the type of surfactant are both statistically significant for the mean, d10, and d90 particle sizes on 99% confidence level. 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.

The DOE #4 investigation has shown that the impinging jets system produced crystals with slightly smaller mean particle sizes when the amount of HPMC and SDS was increased in the experimental procedure. However, the two-way ANOVA statistical mathematical model found that the amount of HPMC and SDS relative to the amount of griseofulvin present was not statistically significant with regards to mean and d90 particle sizes on 99% confidence level when comparing the two levels investigated in this study. The model did find that it was statistically significantly with regards to d10 particle sizes on 99% confidence level. Thus, the amount of HPMC and SDS has a greater effect on the particle size distribution than the actual mean particle size. DOE #4 also confirmed the findings of the DOE #3 study regarding the performance of sonication power intensity on the precipitation of griseofulvin. The two-way ANOVA statistical

mathematical model of DOE #4 showed the same conclusion regarding sonication power intensity as the two-way ANOVA model of DOE #3.

The results of the effect of jet velocity investigation indicates that the experiments operated with a higher solvent jet velocity produced a slightly smaller mean particle size than the lower solvent jet velocity experiments. However, the d10 and d90 particle sizes were found to be fairly close, but a visual observation of the particle size distributions and SEM micrographs showed that the higher jet velocity experiments produced a greater amount of smaller sized particles. The higher jet velocity experiments introduced more kinetic energy to the point of impingement, and were expected to form smaller particles. However, a more significant study involving a range of solvent jet velocities should be conducted to better understand how this variable effects both the mean particle size and particle size distribution. At the moment, it can only be concluded that the higher jet velocity does offer an advantage over the lower jet velocity, but it is not known if this advantage is significant enough to warrant the higher equipment and materials cost associated with achieving this higher jet velocity, especially when sonication offers a much higher amount of energy.

XRD analysis was conducted on experimental samples from all of the experimental conditions investigated in Chapter 3. The XRD results showed that samples of griseofulvin were fully crystalline, and the crystal habit of griseofulvin was the same irrespective of the experimental conditions.

CHAPTER 4

CRYSTAL PRECIPITATION WITHIN SONICATED CONFINED IMPINGING JETS MIXING SYSTEM

4.1 Experimental Materials, Equipment and Methods

4.1.1 Materials

The materials used in this portion of the work are the same as those listed in Chapter 3.

4.1.2 Experimental Apparatus

The design of the experimental apparatus used in this study is completely original. It was created to couple the reproducibility and effectiveness of the confined impinging jets of Midler et. al. [16] and the power and energy of ultrasonics. A schematic of the experimental system is shown in Figure 4.1. The actual experimental setup in the laboratory .is shown in Figure 4.2. Two jacketed 1-liter reservoirs contained the drug solution (Griseofulvin in acetone) and the anti-solvent solution (aqueous solution of HPMC and SDS) separately. The reservoir with the anti-solvent solution was jacketed and its content was cooled by circulating cold water through the jacket using an external water bath provided with a pump (Endocal RTE-110, Neslab Instruments Inc., Newington, New Hampshire). The drug solution did not have to be heated or cooled. Therefore, the corresponding reservoir was not connected to any water bath.

Each reservoir was connected to a gear pump through a recirculation loop made of stainless steel piping, using ½ inch diameter high-density polyethylene (HDPE) tubing, which then fed the impinging jet assembly downstream. These pumps were a Lobee 2LOE-S (Lobee Pump & Machinery Company, Gasport, New York) for the anti-solvent solution, and a Shertech GPST2 (Hypro Industrial Products Group, New Brighton,

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Minnesota) for the drug solution. The flow rates of each solution passing through the gear pumps were controlled by adjusting the recirculation flow around the gear pumps through respective globe valves (CF8M, ½ inch diameter, Sharpe Valves, Northlake, Illinois). Two identical rotameters (65mm stainless steel Gilmont Accucal Flowmeters, Gilmont Instrument Company, Barrington, Illinois) with borosilicate glass floats were used to monitor the flow rates of the anti-solvent and solvent solutions.



Figure 4.1 Schematic of ultrasonic confined impinging jets experimental system.



Figure 4.2 Ultrasonic confined impinging jets experimental system within the laboratory.

The impinging jet assembly consisted of two stainless steel jet nozzles arranged diametrically opposed to each other with the outlet tips of the nozzles directed to face each other. The jet nozzles had 0.508 mm (0.020 inch) internal diameters, and 1.59 mm (0.0625 inch) outer diameters. The liquid streams from these nozzles impinged within a small custom-made polyetheretherketone (PEEK) chamber. This chamber was constructed by George Barnes, machinist in the Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering Department at NJIT. The chamber was cylindrical in shape and contained four holes. Two of these holes were for the opposing fluid jet nozzles entering the chamber from the sides and had diameters of 1.59 mm (0.0625 inch), which was the same as the outer diameter of the jet nozzles. The distance between the two jet nozzles was 7 mm. Another hole was at the bottom of the chamber and acted as the fluid outlet and had a diameter of 4.72 mm(0.186 inch). The final larger hole was for the insertion of the sonicator probe at the top of the chamber and had a

diameter of 12.7 mm (0.5 inch). An ethylene propylene diene M-class rubber (EPDM) gasket was used to seal the chamber at the top around the sonicator probe. Figure 4.3 displays an image of the custom-made chamber. The chamber had a volume of 1.93 mL without the sonicator probe in place, and 1.53 mL with the sonicator probe in place. This volume included the outlet cylinder.





Figure 4.3 Custom-made impinging jets chamber.

The sonication probe placed in the top hole of the chamber, as pictured in Figure 4.3, was connected to a 250 W sonicator (Omni Ruptor 250 Ultrasonic Homogenizer, Model #OR250-115, Omni International, Inc., Marietta, GA). The probe tip used in this study was the 3/8 inch Processing Tip. The 3/8 inch Processing Tip (Model #OR-T-375, Omni International, Inc., Marietta, GA) had a diameter of 9.5 mm (0.375 inch) and could operate at the maximum level of 250 W.

4.1.3 Experimental Procedure

4.1.3.1 Preparation of Drug Solution

A weighed amount of Griseofulvin (usually 8.4 g of drug for 200 mL of acetone or 10.5 g of drug for 250 mL of acetone) was transferred to a volumetric flask and the required volume of acetone was added to it. The flask was then placed in a sonication bath to dissolve the drug in acetone (typically 1 hour). The drug solution was stored at room temperature. The resulting concentration of Griseofulvin in acetone was 42 g/L. This solution was used as a feed solution in all experiments.

4.1.3.2 Preparation of Antisolvent Solution

A stock solution was prepared by transferring 700 mL of distilled water to a 2-L Erlenmeyer flask, and then heating and stirring the flask with a magnetic stirrer on a hotplate (Jenway 1000, Essex, UK) until the temperature reached 75°C. Then, 1.5 g of HPMC was added while stirring. After 5 minutes, heating was stopped and 700 mL of distilled water was added. When the solution was sufficiently cooled (50°C), 1.5 g of SDS was added. Stirring was continued for 5 minutes, and then 600 mL of distilled water was added to make 2 Liter of a stock solution. The concentrations of HPMC and SDS in the final solution were both 0.075%W/V. The solution was capped and stored in the same Erlenmeyer flask at room temperature until needed.

4.1.3.3 Impinging Jet Crystallization Process

The anti-solvent reservoir was filled with 1 L of the anti-solvent solution. The water bath for the anti-solvent reservoir was switched on and run for at least 1 hour before the experiments started so that the anti-solvent temperature was low enough (4°C) for the experiment.

After checking the alignment of the jets (visually) so that they would point to each other at 180° and the distance between the nozzles remained 7 mm, the jet assembly was connected to the rest of the experimental system. The flow rate of both jets had been adjusted prior to the experiment by passing acetone or distilled water through the jets so that the desired impinging jet velocity was obtained. The flow rate of the solvent stream was maintained at a constant 32.3 mL/min, which corresponded in a consistent solvent jet velocity at 2.66 m/s for all experiments. However, the anti-solvent jet velocity varied depending on the experimental conditions used. In order to observe the effect of the mass flow ratio between the anti-solvent and solvent streams on the resulting particle size and particle size distribution, the anti-solvent stream flow rate ranged from 84.6 to 357 mL/min (corresponding jet velocity range of 6.96 m/s to 29.36 m/s). The sonication probe was placed through the hole at the top of the chamber, as shown in Figure 4.3. The power of the sonicator ranged from 0 to 250 W depending on the experimental conditions.

When the anti-solvent solution was sufficiently cooled, the drug solution was placed in its reservoir tank and both the drug solution and the anti-solvent solution were forced to pass through the jets by turning on the gear pumps simultaneously. Once the pumps were activated, the sonicator was turned on as well. This is performed very quickly, and only takes few seconds to turn on the pumps and sonicator. The product stream of the chamber emptied into a 1000 mL glass beaker. The experiment was stopped as soon as drug solution ran out. A typical experiment ran between 1 and 5 minutes depending on the flow rates used.

4.1.4 Experimental Approach

4.1.4.1 Design of Experiments (DOE) Approach

A Design of Experiments (DOE) approach was also used in for the confined impinging jets experimental study. A description and explanation of a DOE approach is found in Section 3.1.3.1. For this study, only one single DOE study was conducted. The DOE study consisted of two factors: antisolvent-to-solvent mass flow ratio, and sonication power. Other important experimental parameters that were studied in the submerged impinging jets experimental study were kept constant. The values for these parameters were consistent with the best results displayed in the submerged impinging jets experimental study. Table **4.1** below summarizes the number of levels for each factor.

Table 4.1 The factors and their accompanying levels for the confined impinging jetDOE investigation.

Sonication Power	Antisolvent-to-Solvent Mass Flow Ratio					
	3.32:1	5.64:1	8.11:1	9.64:1	11.01:1	13.99:1
0 W						
75 W						
125 W						
200 W						
250 W						

4.1.5 Analytical Methods

4.1.5.1 Particle Size Distribution Determination via Light Scattering

Samples were collected at the end of each experiment by pouring the contents of the 1000 mL glass beaker into 50 mL centrifugal vials. The samples were collected in multiple centrifugal vials to check for homogenous distribution as well as error in the analytical

method and their particle size distribution was determined immediately by using a Beckman Coulter LS230 particle size analyzer apparatus (Beckman Coulter LS230, Beckman Coulter, Inc., Fullerton, California). These samples were used as such, without any dilution. The LS230 apparatus measures particle volume distribution using both Fraunhofer and Mie light scattering. It can measure particle sizes ranging from 0.04 μ m to 2000 μ m. A sample was circulated through a sample cell at constant speed, and as a beam of laser light passed through the sample it was diffracted by the particles within the sample and the scattered light was collected by series of detectors. A 100% de-ionized water solution was used as the background fluid during operation of the LS230 apparatus. Each sample was analyzed at least 2 times to check for any error. These multiple data are averaged and used for further investigation.

4.1.5.2 Structural Analysis by Scanning Electron Microscopy (SEM)

A scanning electron microscope (LEO 1520 VP FESEM, Zyvex Instruments, Richardson, Texas) was used to perform the detailed structural analysis of the samples. Particle size and morphology were studied. SEM stubs were prepared by adding few drops of the suspension from the centrifugal vials collected for LS analysis. At least two stubs were prepared for the each experiment performed. Each stub was placed under vacuum in desiccators to dry the sample. Micrographs of different regions of the stub were taken and analyzed. An analysis technique which combines the secondary electron (SE) signal and the backscattered-electron (BE) signal was used for each of the samples. With this analysis technique, the user can easily switch between the two signals separately or combine the two at varying percentages to gain the desired detail in the images. The SE signal masks the compositional information of the sample by the dominant topographic search for phases of interest. This provides clearer, more detailed sample images at higher magnification powers. While, the BE signal obtains a great deal of compositional information (atomic-number contrast) which dominates the topographic information. Since the primary feature of the BE signal is the distribution of phases of different average atomic number, samples of containing different atomic components visually appear differently in the images. Thus, combining the two signals helps to utilize the advantages of both signals. The samples were analyzed using the Robinson Backscattered Detector (RBSD), with an accelerating voltage of 5 keV, and a working distance of 7-8 mm. During operation, the RBSD was placed into position over the sample. The RBSD is a wide-angle scintillator photomultiplier type of backscattering detector comprised of an arm of scintillation material with a hole through which the electron beam passes.

4.2 **Results and Discussion**

Two major experimental parameters were studied in this work: the effect of the antisolvent-to-solvent mass flow ratio on the mean particle size and particle size distribution, and the effect of sonication power on the mean particle size and particle size distribution.

4.2.1 Effect of Antisolvent-to-Solvent Mass Flow Ratio

In order to understand the effect of the antisolvent-to-solvent mass flow ratio, twelve experiments at six different mass flow ratios were conducted using the ultrasonic confined impinging jets apparatus shown in Figure 4.2. 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. No sonication was used during the experiments, and the sonicator probe was not part of these experiments. The temperature of the solvent stream was maintained between 23-27 °C, while the antisolvent stream temperature was maintained between 3-5 °C. On the other hand, the antisolvent flow rate was adjusted. The six antisolvent flow rates used were: 84.6 mL/min (6.96 m/s corresponding jet velocity), 144 mL/min (11.84 m/s), 207 mL/min (17.02 m/s), 246 mL/min (20.23 m/s), 281 mL/min (23.11 m/s), and 357 mL/min (29.36 m/s). This resulted in the following six antisolvent-to-solvent mass flow ratios: 3.32-to-1, 5.64-to-1, 8.11-to-1, 9.64-to-1, 11.01-to-1, and 13.99-to-1. Replicates were run for the 8.11-to-1, 9.64-to-1, and 11.01-to-1 cases. For each experiment, the particle size distribution was determined multiple times with the Beckman-Coulter LS230 apparatus, and the results averaged accordingly. The individual particle size distributions of each experimental condition investigated and their accompanying SEM micrographic images can be found in Appendix D (Figures D.1.1-D.1.6).

Figure 4.4 shows the crystal size distribution for experiments conducted at an antisolvent-to-solvent mass flow ratio of 3.32-to-1 and no sonication present. The particle size distribution ranged from a minimum of 1-2 μ m to a maximum of 125 μ m. The d10 particle size was found to be 17 μ m, and the d90 particle size was found to be 75.03 μ m. The mean particle size was found to be 45.14 μ m. The particle size distribution was comparable in all experimental samples. An SEM micrograph for the experiment is shown in Figure 4.5. The crystals were present in two different shapes in the SEM micrographs. The shape that accounted for the greatest volume was the elongated and rod-like crystals. These particles appeared to be around the size of the

mean particle size, with some slightly smaller and some slightly greater. The rod-like crystals accounted for the largest particles in the SEM micrographs. The other crystals were less elongated and tetragonal bipyramidal in shape. These crystals account for the smaller particle sizes found in the SEM micrographs with sizes along the lines of $10 \mu m$.



Figure 4.4 Particle size distribution of griseofulvin crystals measured with Beckman-Coulter LS230 apparatus. Antisolvent-to-solvent mass flow ratio of 3.32-to-1, and no sonication present.



Figure 4.5 Electron micrographic image of griseofulvin crystals measured with the SEM apparatus. Antisolvent-to-solvent mass flow ratio of 3.32-to-1, and no sonication present.

Figure 4.6 shows the crystal size distribution for experiments conducted at an antisolvent-to-solvent mass flow ratio of 13.99-to-1 and no sonication present. The particle size distribution ranged from a minimum of 1-2 μ m to a maximum of 50 μ m. The d10 particle size was found to be 4.376 μ m, and the d90 particle size was found to be 33.09 μ m. The mean particle size was found to be 16.36 μ m. The particle size distribution was comparable in all experimental samples. An SEM micrograph for the experiment is shown in Figure 4.7. The crystals were present in two different shapes in the SEM micrographs. The shape that accounted for the greatest volume was the elongated and rod-like crystals. These particles appeared to be around the size of the mean particle size and greater. The rod-like crystals accounted for the largest particles in the SEM micrographs. The other crystals were less elongated and tetragonal bipyramidal

in shape. These crystals account for the smaller particle sizes found in the SEM micrographs with sizes along the lines of $5-6 \,\mu\text{m}$.



Figure 4.6 Particle size distribution of griseofulvin crystals measured with Beckman-Coulter LS230 apparatus. Antisolvent-to-solvent mass flow ratio of 13.99-to-1, and no sonication present.



Figure 4.7 Electron micrographic image of griseofulvin crystals measured with the SEM apparatus. Antisolvent-to-solvent mass flow ratio of 13.99-to-1, and no sonication present.

The effect of antisolvent-to-solvent mass flow ratio on particle size is shown in Figures 4.8 (mean particle size), 4.9 (d10 particle size) and 4.10 (d90 particle size). In each figure the antisolvent-to-solvent mass flow ratio was the parameter of interest. The bars in these figures represent the standard error of replicate experiments.

A number of conclusions can be obtained from an examination of these figures. In general, the mean particle size was found to be relatively large (i.e., of the order of tens of μ m) irrespective of the antisolvent-to-solvent mass flow ratio. As the antisolvent-to-solvent mass flow ratio increased, the mean particle size decreased until an asymptotic value was reached. At ratios above 8.11-to-1, the mean particle size appeared to level off around 20 μ m. Figure 4.9 shows the effect of antisolvent-to-solvent mass flow ratio on

d10 particle size, i.e., the size below which 10% of the particles are found (by volume). This figure clearly shows that the antisolvent-to-solvent mass flow ratio has an appreciable effect on the d10 particle size below ratios of 8.11-to-1. However, at antisolvent-to-solvent mass flow ratios above 8.11-to-1, minimal or no differences exist between the curves for d10 particle size.

By contrast, Figure 4.10 shows that the effect of antisolvent-to-solvent mass flow ratio on the d90 particle size, i.e., the size below which 90% of the particles are found (by volume), is more pronounced. This figure shows that the antisolvent-to-solvent mass flow ratio has a significant effect on the d90 particle size. As the antisolvent-to-solvent mass flow ratio increases, the d90 particle size decreases, thus resulting in narrow particle size distribution.



Figure 4.8 Mean particle size as a function of antisolvent-to-solvent mass flow ratio.



Figure 4.9 d10 particle size as a function of antisolvent-to-solvent mass flow ratio.



Figure 4.10 d90 particle size as a function of antisolvent-to-solvent mass flow ratio.

4.2.2 Effect of Sonication Power

In order to quantify the effect of the sonication power, fifty experiments at five different sonication powers were conducted using the ultrasonic confined impinging jets apparatus shown in Figure 4.2. 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 temperature of the solvent stream was maintained between 23-27 °C, while the antisolvent stream temperature was maintained between 3-5 °C. In a similar fashion to the previous investigation, the antisolvent flow rate was adjusted, and the same six antisolvent flow rates were used. This resulted in the following six antisolvent-to-solvent mass flow ratios: 3.32-to-1, 5.64-to-1, 8.11-to-1, 9.64-to-1, 11.01-to-1, and 13.99-to-1. The sonication power being emitted by the sonicator probe was adjusted according to the experiments. The five different sonication powers used here were 0 W, 75 W, 125 W, 200 W, and 250 W. For the cases involving no sonication power, the sonicator probe was not inserted into the chamber, and the top of the chamber was closed off with a gasket made from EPDM. For the other four cases, the sonicator probe was placed into the chamber just above the impinging jet nozzles. Each of these five sonication powers were run for each of the six antisolvent-to-solvent mass flow ratios. Replicates were run for the 8.11-to-1, 9.64-to-1, and 11.01-to-1 mass flow ratios at 0 W of power; 13.99-to-1 mass flow ratio at 75 W of power; 5.64-to-1 and 8.11-to-1 mass flow ratios at 125 W of power; 13.99-to-1 mass flow ratio at 200 W of power; and 8.11-to-1, 11.01-to-1, and 13.99-to-1 mass flow ratios at 250 W of power cases. For each experiment, the particle size distribution was determined multiple times with the Beckman-Coulter LS230
apparatus, and the results averaged accordingly. The individual particle size distributions of each experimental condition investigated and their accompanying SEM micrographic images can be found in Appendix D (Figures D.2.1-D.7.4).

Figure 4.11 shows the crystal size distribution for experiments conducted at an antisolvent-to-solvent mass flow ratio of 9.64-to-1 and no sonication present. The particle size distribution ranged from a minimum of 1-2 µm to a maximum of around 100 μ m. The d10 particle size was found to be 5.946 μ m, and the d90 particle size was found to be 50.77 μ m. The mean particle size was found to be 26.89 μ m. The particle size distribution was comparable in all experimental samples. An SEM micrograph for the experiment is shown in Figure 4.12. The crystals were present as elongated rod-like crystals in the SEM micrographs. These particles ranged from shorter, thinner rods, with particle sizes around the mean of the distribution and smaller, to longer, thicker rods, with particle sizes around the d90 of the distribution and few above. The average mean particle size calculated from the three experimental replicates was found to be $25.99 \ \mu m$. The standard error in the mean particle size between these experiments was rather small at 0.619 μ m. The averaged d10 particle size was also calculated for the three replicates. The averaged d10 particle size was 5.767 μ m. The standard error in the d10 particle size was also small at 0.185 μ m. The averaged d90 particle size was found to be 51.38 μ m, and the standard error of the d90 particle size was $0.810 \,\mu m$.



Figure 4.11 Particle size distribution of griseofulvin crystals measured with Beckman-Coulter LS230 apparatus. Antisolvent-to-solvent mass flow ratio of 9.64-to-1, and no sonication present.



Figure 4.12 Electron micrographic image of griseofulvin crystals measured with the SEM apparatus. Antisolvent-to-solvent mass flow ratio of 9.64-to-1, and no sonication present.

Figure 4.13 shows the crystal size distribution for experiments conducted at an antisolvent-to-solvent mass flow ratio of 9.64-to-1 and 250 W of sonication power present. The particle size distribution ranged from a minimum of around 0.7 μ m to a maximum of around 7 μ m. The d10 particle size was found to be 1.114 μ m, and the d90 particle size was found to be 3.222 μ m. The mean particle size was found to be 1.980 μ m. The particle size distribution was comparable in all experimental samples. An SEM micrograph for the experiment is shown in Figure 4.14. The crystals were present as elongated rod-like shapes in the SEM micrographs. The elongated rod-shaped crystals seen in the SEM micrographs accounted for the tight range of sizes of the particle size distribution in Figure 4.13.



Figure 4.13 Particle size distribution of griseofulvin crystals measured with Beckman-Coulter LS230 apparatus. Antisolvent-to-solvent mass flow ratio of 9.64-to-1, and 250 W of sonication power present.



Figure 4.14 Electron micrographic image of griseofulvin crystals measured with the SEM apparatus. Antisolvent-to-solvent mass flow ratio of 9.64-to-1, and 250 W of sonication power present.

The effect of sonication power on particle size is shown in Figures 4.15 (mean particle size), 4.16 (d10 particle size) and 4.17 (d90 particle size). In each figure the sonication power in watts was the parameter of interest. The bars in these figures represent the standard error of replicate experiments.

A number of conclusions can be obtained from an examination of these figures. In the absence of sonication, the mean particle size was found to be, in general, very large irrespective of the antisolvent-to-solvent mass flow ratio. The introduction of sonication, even at sonication powers as low as 75 W, appreciably reduced the particle sizes. However, the effect of sonication largely disappeared or even resulted in larger particle sizes (as shown in the curve for a 5.64-to-1 mass flow ratio) when the sonication power was larger than ~ 100 to 150 W. The combination of power and high mass flow ratio (~ 10 -to-1 or larger) appeared to be the most beneficial.

Figure 4.16 shows the effect of sonication power on d10 particle size, i.e., the size below which 10% of the particles are found (by volume). This figure clearly shows that the introduction of sonication helps to reduce the d10 particle size. However, at antisolvent-to-solvent mass flow ratios above 8.11-to-1, minimal or no differences exist between the curves for d10 particle size. In addition, once the sonication power is at or above 75 W d10 remains relatively uniform irrespective of both antisolvent-to-solvent mass flow ratio and sonication power.

By contrast, Figure 4.17 shows that the effect of sonication power on the d90 particle size, i.e., the size below which 90% of the particles are found (by volume), is more pronounced. At lower sonication power, this is likely to be the result of agglomeration effects, which have a greater impact on larger particles rather than smaller particles. At higher sonication powers the d90 curves show a somewhat larger deviation.



Figure 4.15 Mean particle size as a function of sonication power.



Figure 4.16 d10 particle size as a function of sonication power.



Figure 4.17 d90 particle size as a function of sonication power.

4.2.3 Two-way ANOVA Statistical Mathematical Model

In addition to Figures 4.8 and 4.15, the data for the mean particle size were subjected to a two-way ANOVA (analysis of variance) with the following mathematical model:

$$Y_{ijk} = \mu + P_j + M_j + PM_{ij} + \varepsilon_{k(ij)}$$

$$\tag{16}$$

Where P is sonication power treatment,

M is antisolvent-to-solvent mass flow ratio,

i = 1, 2, 3, 4, 5 for the five levels of sonication power

j = 1, 2, 3, 4, 5, 6 for the six values of mass flow ratio

k =for the number of observations in each i, j treatment combination

 $\varepsilon_{k(ij)}$ = the error within each of the treatment combinations.

The ANOVA summary can be found in Table **4.2**. According to the ANOVA results, the sonication power intensity and the antisolvent-to-solvent mass flow ratio are both statistically significant on 99% confidence level.

	df	F	р	
Power				
(P)	4	21.36581	3.58624E-08	significant
Mass				
Flow				
Ratio (M)	5	29.84969	2.12466E-10	significant
				not
PxM	20	1.522542	0.150114104	significant
error	28			
total	57			

Table 4.2 Summary of two-way ANOVA for ultrasonic confined impinging jets DOEmean particle size investigation.

In addition to Figures 4.9 and 4.16, the data for the d10 particle size were subjected to a two-way ANOVA (analysis of variance) with the same mathematical model as Equation 16.

The ANOVA summary can be found in Table **4.3**. According to the ANOVA results, the sonication power intensity, the antisolvent-to-solvent mass flow ratio, and the interaction between the two factors are statistically significant on 99% confidence level.

	df	F	р	
Power (P)	4	42.66143	1.59198E-11	significant
Mass Flow Ratio (M)	5	19.91039	1.91606E-08	significant
PxM	20	3.114072	0.002959626	significant
error	28			
total	57			

Table 4.3 Summary of two-way ANOVA for ultrasonic confined impinging jets DOEd10 particle size investigation.

In addition to Figures 4.10 and 4.17, the data for the d10 particle size were subjected to a two-way ANOVA (analysis of variance) with the same mathematical model as Equation 16.

The ANOVA summary can be found in Table **4.4**. According to the ANOVA results, the sonication power intensity and the antisolvent-to-solvent mass flow ratio are both statistically significant on 99% confidence level.

Table	4.4	Summary of two-way	ANOVA	for	ultrasonic	confined	impinging	jets DO	E
d90 par	rticle	e size investigation.							

	df	F	р	
Power		_		
(P)	4	8.592026	0.000117758	significant
Mass				
Flow				
Ratio (M)	5	31.93849	9.66997E-11	significant
				not
PxM	20	0.063874	0.999999983	significant
error	28			
total	57			

4.3 Conclusions for this Chapter

In this portion of the work, the effect of antisolvent-to-solvent mass flow ratio and sonication power on the anti-solvent precipitation of griseofulvin in a new innovative ultrasonic confined impinging jet system was experimentally determined. Six separate antisolvent-to-solvent mass flow ratios and five different sonication powers were investigated. Both of these parameters were seen as important aspects of understanding the capabilities of the new ultrasonic confined impinging jet apparatus.

As seen from the experimental results, the antisolvent-to-solvent mass flow ratio strongly affects mean particle size and particle size distribution. As the antisolvent-tosolvent mass flow ratio increases, the mean particle size decreases and the particle size distribution narrows. The increase in the amount of antisolvent solution present most likely enhances the level of supersaturation and results in the smaller mean particle size and narrow particle size distribution.

Sonication power also strongly affects the mean particle size and particle size distribution of the experimental results. Each of the six antisolvent-to-solvent mass flow ratios showed drastic improvements at increased sonication powers. The introduction of sonication to the system offers much smaller mean particle sizes and narrow particle size distributions that could not be achieved for the griseofulvin antisolvent crystallization process with confined impinging jets alone. At higher antisolvent-to-solvent mass flow ratios and higher sonication powers, comparable mean particle sizes and particle size distributions are produced.

A two-way ANOVA statistical mathematical model was utilized to analysis the experimental mean, d10, and d90 particle sizes. According to the ANOVA results, the

sonication power intensity and the antisolvent-to-solvent mass flow ratio are both statistically significant with regards to the mean, d10, and d90 particle sizes on 99% confidence level. In addition, the interaction of the two factors was found to be statistically significant with regards to d10 particle size on 99% confidence level. These ANOVA results confirm that the sonication power intensity and the antisolvent-to-solvent mass flow ratio have a significant effect on the mean particle size and particle size distribution during the precipitation of griseofulvin.

The new ultrasonic confined impinging jet system offers a truly continuous antisolvent crystallization process. It has shown to be highly controllable as it has produced highly reproducible results in the case of griseofulvin antisolvent crystallization. The sonication power input can be controlled which in turn allows for adjustable resulting particle size. Small mean particle sizes between 1-2 μ m with narrow particle size distributions were accomplished in the griseofulvin antisolvent crystallization case using the ultrasonic confined impinging jet system. These are distinct advantages over other systems currently used for crystallization.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE WORK

5.1 Conclusions

In this work, the fluid dynamics of the typical reactor configurations used in the pharmaceutical industry, i.e., unbaffled and partially baffled tank reactors provided with a retreat-blade impeller, was thoroughly studied and analyzed from both a computational and experimental point-of-view using CFD and LDV. In both cases, two systems were studied, i.e., one with a flat-bottom tank and another with a hemispherical-bottom tank. The following conclusions can be derived from the results obtained in this portion of the study:

- In all the systems investigated here, the tangential component of the velocity appears to dominate the flow over the axial and radial components.
 - The highest tangential velocity is typically about 35% of the impeller tip speed for the baffled case and about 47% of the impeller tip speed for the unbaffled case, irrespective of the type of tank bottom.
 - The axial component of the velocity is always significantly smaller than the tangential component, and is on the order of 5-15% of the impeller tip speed, with the higher value obtained in the baffled configuration.
 - The radial component of the velocity was found to be the smallest of the three, with velocity magnitudes ranging from 0-10% of the impeller tip speed.

- The presence of a hemispherical bottom instead of a flat bottom did not significantly alter the velocity profiles above the impeller, when similarly baffled systems were compared. However, this was not entirely the case below the impeller, where the presence of the hemispherical bottom resulted in a slightly larger down-flow next to the wall.
- The dominance of the tangential velocity and the small value of the radial velocity and especially axial velocity in all the system investigated here indicate a poor vertical recirculation of the fluid inside the tank and therefore a reduced mixing efficiency for this type of reactors.
- The experimental results obtained in this work compare favorably with the experimental results and the computational predictions obtained previously in this laboratory. However, discrepancies exist in the axial and radial components of the velocity due to their small magnitudes and the systems' very high sensitivity to small geometric difference. The small velocity magnitudes in the axial and radial directions amplify this error.
- Together with recent data obtained in this laboratory, the data presented here constitute the first detailed mapping of the flow distribution inside a system of significant industrial importance that has not been studied to any significant extent before. It is expected that this work can contribute to a better understanding of the way in which these reactors operate and help their users operate them more effectively.
- Finally, the results of fluid dynamic simulation and experimental results obtained here helped identify the optimal location of the impinging jets within

the stirred-tank reactor. Accordingly, the best location in a glass-lined reactor system with a retreat blade impeller where the jets should be located would be on the same radial plane as the impeller tip, where the fluid velocity and turbulence dissipation rate (ε) were at its greatest.

After the fluid dynamics study was completed, work was conducted on the precipitation of griseofulvin within a similar reactor configuration which also incorporated a submerged impinging jets system where the precipitation took place. The following conclusions can be derived from the results obtained in portion of this study:

- The precipitation of griseofulvin micro/nanoparticles was successfully achieved by the antisolvent crystallization method using the impinging jets mixer.
- A comparison between the results of the impinging jets experiments operated in air and those obtained with jets submerged in distilled water shows that the submerged impinging jets case produce particles with a smaller mean particle size, and a slightly tighter particle size distribution. This is most likely due to the larger supply of antisolvent in the submerged case, which would allow for a more rapid, complete precipitation of the griseofulvin.
- Experiments based on a Design of Experiment approach (DOE #1) has shown that:
 - The impinging jets system produced crystals with smaller mean particle sizes when the two jets were oriented 180 degrees apart and pointed directly at each other than when the two jets were oriented in a 120 degree configuration.

- More significantly, the introduction of ultrasonic power at the impingement point resulted in markedly smaller mean particle size and a tighter particle size distribution.
- \circ The addition of sonication and presence of Tween[®] 80 to the impinging jets experiments helped to reduce the mean particle size from above 100 μm to below 15 μm.
- Thus, it was determined that an angle of impingement of 180 degrees, the presence of sonication, and the presence of a surfactant were critical parameters for the rapid precipitation of griseofulvin.
- Additional experiments based on a Design of Experiment approach (DOE #2) has shown that:
 - The impinging jets system produced crystals with smaller mean particle sizes when a large temperature difference was introduced between the two process streams.
 - The control of the experimental temperature helped to enhance supersaturation and provide a tighter particle size distribution.
 - This investigation confirmed the conclusion of DOE #1 in that the addition of sonication to the process resulted in markedly smaller mean particle size and a tighter particle size distribution.
 - Thus, it was concluded that the experimental temperature should be carefully controlled, and a large temperature difference between the solvent and antisolvent streams is desired.

- A comparison of the results of the single jet stream experiments with those of the two jet streams investigation clearly shows that the experiments operated with a single submerged solvent jet stream failed to meet the performance of the two submerged impinging jets system.
- Additional experiments based on a Design of Experiment approach (DOE #3) has shown that:
 - The impinging jets system produced crystals with smaller mean particle sizes when a combination of HPMC and SDS was mixed with the antisolvent solution than when the Tween 80 mixture was used.
 - The HPMC and SDS mixture experiments showed smaller mean particle sizes and tighter, smaller particle size distributions for all sonication power intensities investigated.
 - 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.
 - \circ Such asymptotic values of the particle size were only partially affected by the surfactant used, with mean asymptotic particles sizes on the order of 2-4 μ m for the HPMC and SDS combination and 6-8 μ m for the Tween 80 mixture.

- A two-way ANOVA statistical model showed that the sonication power intensity and the type of surfactant are both statistically significant for the mean, d10, and d90 particle sizes on 99% confidence level.
- 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.
- Additional experiments based on a Design of Experiment approach (DOE #4) has shown that:
 - The impinging jets system produced crystals with slightly smaller mean particle sizes when the concentration of HPMC and SDS in the antisolvent was increased. However, the two-way ANOVA statistical mathematical model found that the amount of HPMC and SDS relative to the amount of griseofulvin present was not statistically significant with regards to mean and d90 particle sizes on 99% confidence level when comparing the two levels investigated in this study. The model did find that it was statistically significantly with regards to d10 particle sizes on 99% confidence level. Thus, the amount of HPMC and SDS has a greater effect on the particle size distribution than the actual mean particle size.
 - DOE #4 also confirmed the findings of the DOE #3 study regarding the performance of sonication power intensity on the precipitation of griseofulvin. The two-way ANOVA statistical mathematical model of

DOE #4 showed the same conclusion regarding sonication power intensity as the two-way ANOVA model of DOE #3.

- The results of the effect of jet velocity investigation indicates that the experiments conducted at a higher solvent jet velocity produced a slightly smaller mean particle size than the lower solvent jet velocity experiments. However, the d10 and d90 particle sizes were found to be in close proximity, but visual observation of the particle size distributions and SEM micrographs showed that the higher jet velocity experiments produced a greater amount of smaller sized particles.
- The higher jet velocity experiments introduced more kinetic energy to the point of impingement, and were expected to form smaller particles. However, a more significant study involving a range of solvent jet velocities should be conducted to better understand how this variable effects both the mean particle size and particle size distribution.
- At the moment, it can only be concluded that the higher jet velocity does offer an advantage over the lower jet velocity, but it is not known if this advantage is significant enough to warrant the higher equipment and materials cost associated with achieving this higher jet velocity, especially when sonication generates a much higher amount of energy dissipation.
- XRD analysis was conducted on samples obtained from experiments under all the experimental conditions investigated for the submerged impinging jet case. The XRD results showed that samples of griseofulvin were fully crystalline, and

that the crystal habit of griseofulvin was the same irrespective of the experimental conditions.

After the submerged impinging jets study was completed, another study on the precipitation of griseofulvin was conducted using a newly developed ultrasonic confined impinging jets system as the crystallizer. The following conclusions can be derived from the results obtained in this portion of the study:

- The effect of antisolvent-to-solvent mass flow ratio and sonication power on the anti-solvent precipitation of griseofulvin was experimentally determined for a newly developed ultrasonic confined impinging jet system.
- As seen from the experimental results, the antisolvent-to-solvent mass flow ratio strongly affects mean particle size and particle size distribution. As the antisolvent-to-solvent mass flow ratio increases, the mean particle size decreases and the particle size distribution narrows.
- The increase in the amount of antisolvent solution most likely enhances the level of supersaturation at the impingement point and results in the smaller mean particle size and narrow particle size distribution.
- Sonication power also strongly affects the mean particle size and particle size distribution.
- The mean particle size decreased significantly with increased sonication powers for all antisolvent-to-solvent mass flow ratios.
- The introduction of sonication results in much smaller mean particle sizes and narrow particle size distributions that could not be achieved for the griseofulvin antisolvent crystallization process with a confined impinging jets system alone.

- At higher antisolvent-to-solvent mass flow ratios and higher sonication powers, comparable mean particle sizes and particle size distributions are produced.
- A two-way ANOVA statistical mathematical model was utilized to analysis the experimental mean, d10, and d90 particle sizes. The sonication power intensity and the antisolvent-to-solvent mass flow ratio are both statistically significant with regards to the mean, d10, and d90 particle sizes on 99% confidence level. In addition, the interaction of the two factors was found to be statistically significant with regards to d10 particle size on 99% confidence level.
- These ANOVA results confirm that the sonication power intensity and the antisolvent-to-solvent mass flow ratio have a significant effect on the mean particle size and particle size distribution during the precipitation of griseofulvin.
- The new ultrasonic confined impinging jet system offers a truly continuous antisolvent crystallization process which was highly controllable and produced consistent and reproducible results when used for griseofulvin antisolvent crystallization.
- The sonication power input can be easily controlled, which in turn allows for adjustable particle size of the final crystals.
- Small mean particle sizes between 1-2 μm with narrow particle size distributions were accomplished in the griseofulvin antisolvent crystallization case using the ultrasonic confined impinging jet system.

5.2 **Recommendations for Future Work**

The following are possible suggestions for future work related to the hydrodynamics of unbaffled and partially baffled reactors:

- Mixing time and solid suspension experiments should be conducted to quantify these two important mixing aspects in unbaffled and partially baffled systems.
- The vortex seen experimentally at the liquid surface can be incorporated into the CFD simulations using the Volume of Fluid (VOF) strategy.
- Experimental and computational studies can be performed by varying the following parameters:
 - impeller tip speed
 - impeller bottom clearance
 - o baffle type
 - baffle location
 - o number of baffles.
- An additional type of reactor vessel with a dished bottom can be investigated.

The following are possible suggestions for future work related to precipitation in submerged impinging jets systems:

- Additional API crystallization from different BCS classes could be studied.
- Additional solvent/antisolvent systems could be investigated.
- Additional stabilizing agents could be used.

• A wider range of impinging jet velocities and their effect on particle size could be conducted.

The following are possible suggestions for future work related to precipitation in confined impinging jets systems:

- Different impinging jet velocities could be investigated.
- Different angles of impingement should be studied.
- Varying the chamber configuration and the effect on particle size would be an interesting study.
- Additional API crystallization from different BCS classes could be studied.

APPENDIX A

COMPARISON BETWEEN LDV EXPERIMENTAL RESULTS AND CFD PREDICTIONS

Experimental LDV results and CFD predictions are presented in this Appendix as follows:

Comparison of <u>tangential</u> velocities in the <u>unbaffled</u> , cylindrical, flat-bottom tank	A.1.1.1 – A.1.1.4
Comparison of <u>axial</u> velocities in the <u>unbaffled</u> , cylindrical, flat-bottom tank	A.1.2.1—A.1.2.4
Comparison of <u>radial</u> velocities in the <u>unbaffled</u> , cylindrical, flat-bottom tank	A.1.3.1—A.1.3.4
Comparison of <u>tangential</u> velocities in the <u>single-baffle</u> , cylindrical, flat-bottom tank	A.2.1.1—A.2.1.4
Comparison of <u>axial</u> velocities in the <u>single-baffle</u> , cylindrical, flat-bottom tank	A.2.2.1 – A.2.2.4
Comparison of <u>radial</u> velocities in the <u>single-baffle</u> , cylindrical, flat-bottom tank	A.2.3.1 – A.2.3.4
Comparison of <u>tangential</u> velocities in the <u>unbaffled</u> , cylindrical, hemispherical-bottom tank	A.3.1.1—A.3.1.3
Comparison of <u>axial</u> velocities in the <u>unbaffled</u> , cylindrical, hemispherical-bottom tank	A.3.2.1 – A.3.2.3
Comparison of <u>tangential</u> velocities in the <u>single-baffle</u> , cylindrical, hemispherical-bottom tank	A.4.1.1—A.4.1.3
Comparison of <u>axial</u> velocities in the <u>single-baffle</u> , cylindrical, hemispherical-bottom tank	A.4.2.1—A.4.2.3

A.1 Comparison Between LDV Data and the CFD Prediction in Unbaffled, Flat-Bottom Tank.



A.1.1 Comparison Between LDV Data and CFD Prediction for Tangential Velocities:

Figure A.1.1.1 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 185mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.1.1.2 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 147mm and z = 96mm in the <u>unbaffled</u>, <u>flatbottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.1.1.3 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 78mm and z = 26mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.1.1.4 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 22mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



A.1.2 Comparison Between LDV Data and CFD Prediction for Axial Velocities:

Figure A.1.2.1 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 185mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.1.2.2 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 147mm and z = 96mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.1.2.3 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 78mm and z = 26mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.1.2.4 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 22mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



A.1.3 Comparison Between LDV Data and CFD Prediction for Radial Velocities:

Figure A.1.3.1 Comparison between LDV data and CFD prediction for <u>radial</u> velocities at iso-surfaces z = 185mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.1.3.2 Comparison between LDV data and CFD prediction for <u>radial</u> velocities at iso-surfaces z = 147mm and z = 96mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.1.3.3 Comparison between LDV data and CFD prediction for <u>radial</u> velocities at iso-surfaces z = 78mm and z = 26mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.1.3.4 Comparison between LDV data and CFD prediction for <u>radial</u> velocities at iso-surfaces z = 22mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.

A.2 Comparison Between LDV Data and the CFD Prediction in Single-Baffle, Flat-Bottom Tank.





Figure A.2.1.1 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 185mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.


Figure A.2.1.2 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 147mm and z = 96mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.2.1.3 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 78mm and z = 26mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.2.1.4 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 24mm and z = 22mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



A.2.2 Comparison Between LDV Data and CFD Prediction for Axial Velocities:

Figure A.2.2.1 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 185mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.2.2.2 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 147mm and z = 96mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.2.2.3 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 78mm and z = 26mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.2.2.4 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 24mm and z = 22mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



A.2.3 Comparison Between LDV Data and CFD Prediction for Axial Velocities:

Figure A.2.3.1 Comparison between LDV data and CFD prediction for <u>radial</u> velocities at iso-surfaces z = 185mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.2.3.2 Comparison between LDV data and CFD prediction for <u>radial</u> velocities at iso-surfaces z = 147mm and z = 96mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.2.3.3 Comparison between LDV data and CFD prediction for <u>radial</u> velocities at iso-surfaces z = 78mm and z = 26mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.2.3.4 Comparison between LDV data and CFD prediction for <u>radial</u> velocities at iso-surfaces z = 24mm and z = 22mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.

A.3 Comparison Between LDV Data and the CFD Prediction in Unbaffled, Hemispherical-Bottom Tank.



A.3.1 Comparison Between LDV Data and CFD Prediction for Tangential Velocities:

Figure A.3.1.1 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 185mm in the <u>unbaffled</u>, <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.3.1.2 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 78mm and z = 26mm in the <u>unbaffled</u>, <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.3.1.3 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 22mm in the <u>unbaffled</u>, <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



A.3.2 Comparison Between LDV Data and CFD Prediction for Axial Velocities:

Figure A.3.2.1 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 185mm in the <u>unbaffled</u>, <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.3.2.2 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 78mm and z = 26mm in the <u>unbaffled</u>, <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.3.2.3 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 22mm in the <u>unbaffled</u>, <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.

A.4 Comparison Between LDV Data and the CFD Prediction in Single-Baffle, Hemispherical-Bottom Tank.



A.4.1 Comparison Between LDV Data and CFD Prediction for Tangential Velocities:

Figure A.4.1.1 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 185mm in the <u>single-baffle</u>, <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.4.1.2 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 78mm and z = 26mm in the <u>single-baffle</u>. <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.4.1.3 Comparison between LDV data and CFD prediction for <u>tangential</u> velocities at iso-surfaces z = 24mm and z = 22mm in the <u>single-baffle</u>, <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



A.4.2 Comparison Between LDV Data and CFD Prediction for Axial Velocities:

Figure A.4.2.1 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 185mm in the <u>single-baffle</u>, <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.





<u>bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.



Figure A.4.2.3 Comparison between LDV data and CFD prediction for <u>axial</u> velocities at iso-surfaces z = 22mm in the <u>single-baffle</u>, <u>hemispherical-bottom</u> tank. Error bars represent the standard error from 3 replicate experiments.

APPENDIX B

VELOCITY VECTOR IMAGES FROM CFD SIMULATIONS

Velocity Vector images from the CFD simulations are presented in this Appendix as follows:

Velocity Vector images from CFD simulation of <u>unbaffled</u> , cylindrical, flat-bottom tank	B.1.1 – B.1.4
Velocity Vector images from CFD simulation of <u>single-baffle</u> , cylindrical, flat-bottom tank	B.2.1 – B.2.6
Velocity Vector images from CFD simulation of <u>unbaffled</u> , cylindrical, hemispherical-bottom tank	B.3.1 – B.3.5
Velocity Vector images from CFD simulation of <u>single-baffle</u> , cylindrical, hemispherical-bottom tank	B.4.1 – B.4.6



B.1 Velocity Vector Images from CFD Simulation of Unbaffled, Flat-Bottom Tank.

Figure B.1.1 Front view and side view of velocity vectors from CFD simulation at isosurface rz-plane in the <u>unbaffled</u>, <u>flat-bottom</u> tank.



Figure B.1.2 Velocity vectors of CFD simulation at iso-surfaces z = 185mm and z = 147mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank.



Figure B.1.3 Velocity vectors of CFD simulation at iso-surfaces z = 96mm and z = 78mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank.



Figure B.1.4 Velocity vectors of CFD simulation at iso-surfaces z = 26mm and z = 22mm in the <u>unbaffled</u>, <u>flat-bottom</u> tank.

B.2 Velocity Vector Images from CFD Simulation of Single-Baffle, Flat-Bottom Tank.







Figure B.2.2 Front view and side view of velocity vectors from CFD simulation at isosurface rz-plane ($\theta = \frac{1}{2} \pi$, $\theta = \frac{3}{2} \pi$) in the <u>single-baffle</u>, <u>flat-bottom</u> tank.



Figure B.2.3 Velocity vectors of CFD simulation at iso-surfaces z = 185mm and z = 147mm in the single-baffle, flat-bottom tank.



Figure B.2.4 Velocity vectors of CFD simulation at iso-surfaces z = 96mm and z = 78mm in the <u>single-baffle</u>, <u>flat-bottom</u> tank.



Figure B.2.5 Velocity vectors of CFD simulation at iso-surfaces z = 26mm and z = 24mm in the single-baffle, flat-bottom tank.



Figure B.2.6 Velocity vectors of CFD simulation at iso-surface z = 22mm in the singlebaffle, flat-bottom tank.



B.3 Velocity Vector Images from CFD Simulation of Unbaffled, Hemispherical-Bottom Tank.

Figure B.3.1 Front view and side view of velocity vectors from CFD simulation at isosurface rz-plane in the <u>unbaffled</u>, <u>hemispherical-bottom</u> tank.



Figure B.3.2 Velocity vectors of CFD simulation at iso-surfaces z = 185mm and z = 147mm in the <u>unbaffled</u>, <u>hemispherical-bottom</u> tank.


Figure B.3.3 Velocity vectors of CFD simulation at iso-surfaces z = 96mm and z = 78mm in the <u>unbaffled</u>, <u>hemispherical-bottom</u> tank.



Figure B.3.4 Velocity vectors of CFD simulation at iso-surfaces z = 26mm and z = 24mm in the <u>unbaffled</u>, <u>hemispherical-bottom</u> tank.



Figure B.3.5 Velocity vectors of CFD simulation at iso-surface z = 22mm in the unbaffled, hemispherical-bottom tank.

B.4 Velocity Vector images from CFD simulation of single-baffle, hemispherical-



bottom tank.

Figure B.4.1 Front view and side view of velocity vectors from CFD simulation at isosurface rz-plane ($\theta = 0, \theta = \pi$) in the <u>single-baffle</u>, <u>hemispherical-bottom</u> tank.



Figure B.4.2 Front view and side view of velocity vectors from CFD simulation at isosurface rz-plane ($\theta = \frac{1}{2} \pi$, $\theta = \frac{3}{2} \pi$) in the <u>single-baffle</u>, <u>hemispherical-bottom</u> tank.



Figure B.4.3 Velocity vectors of CFD simulation at iso-surfaces z = 185mm and z = 147mm in the single-baffle, hemispherical-bottom tank.



Figure B.4.4 Velocity vectors of CFD simulation at iso-surfaces z = 96mm and z = 78mm in the single-baffle, hemispherical-bottom tank.



Figure B.4.5 Velocity vectors of CFD simulation at iso-surfaces z = 26mm and z = 24mm in the single-baffle, hemispherical-bottom tank.



Figure B.4.6 Velocity vectors of CFD simulation at iso-surface z = 22mm in the <u>single-baffle</u>, <u>hemispherical-bottom</u> tank.

APPENDIX C

ADDITIONAL PARTICLE SIZE DISTRIBUTIONS AND SEM MICROGRAPHIC IMAGES FOR THE SUBMERGED IMPINGING JETS EXPERIMENTAL STUDY

Particle Size Distribution images from the Beckman-Coulter LS230 and SEM micrographic images for the Submerged Impinging Jets Experimental Study are presented in this Appendix as follows:

Additional experimental results of Submerged Impinging Jets vs Non-submerged Impinging Jets	C.1.1 – C.1.2
Additional experimental results of DOE #1 investigation	C.2.1 – C.2.8
Additional experimental results of DOE #2 investigation	C.3.1 – C.3.4
Additional experimental results of DOE #3 investigation	C.4.1 – C.4.10
Additional experimental results of DOE #4 investigation	C.5.1 – C.5.10



C.1 Additional Experimental Results of Submerged Impinging Jets vs Non-Submerged Impinging Jets

Figure C.1.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by impinging jets in air.



Figure C.1.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets.

C.2 Additional Experimental Results of DOE #1 Experimental Investigation.



Figure C.2.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in distilled water, at 120° angle of impingement, and no sonication.



Figure C.2.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water, at 120° angle of impingement, and no sonication.



Figure C.2.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in distilled water, at 180° angle of impingement, and no sonication.



Figure C.2.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water, at 180° angle of impingement, and no sonication.



Figure C.2.5 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in distilled water, at 120° angle of impingement, and 125 W of sonication.



Figure C.2.6 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water, at 120° angle of impingement, and 125 W of sonication.



Figure C.2.7 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in distilled water, at 180° angle of impingement, and 125 W of sonication.



Figure C.2.8 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water, at 180° angle of impingement, and 125 W of sonication.



C.3 Additional Experimental Results of DOE #2 Experimental Investigation.

Figure C.3.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water with 12°C temperature difference between streams, at 120° angle of impingement, and no sonication.



Figure C.3.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water with 28°C temperature difference between streams, at 120° angle of impingement, and no sonication.



Figure C.3.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water with 12°C temperature difference between streams, at 120° angle of impingement, and 125 W of sonication.



Figure C.3.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water with 28°C temperature difference between streams, at 120° angle of impingement, and 125 W of sonication.



C.4 Additional Experimental Results of DOE #3 Experimental Investigation.

Figure C.4.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water, at 180° angle of impingement, and no sonication.





Figure C.4.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water, at 180° angle of impingement, and no sonication.



Figure C.4.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water, at 180° angle of impingement, and 75 W of sonication.



Figure C.4.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water, at 180° angle of impingement, and 75 W of sonication.



Figure C.4.5 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water, at 180° angle of impingement, and 125 W of sonication.



Figure C.4.6 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water, at 180° angle of impingement, and 125 W of sonication.



Figure C.4.7 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water, at 180° angle of impingement, and 200 W of sonication.



Figure C.4.8 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water, at 180° angle of impingement, and 200 W of sonication.



Figure C.4.9 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of Tween 80 and distilled water, at 180° angle of impingement, and 250 W of sonication.



Figure C.4.10 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water, at 180° angle of impingement, and 250 W of sonication.



C.5 Additional Experimental Results of DOE #4 Experimental Investigation.

Figure C.5.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water with a 5:1:1 drug-to-HPMC-to-SDS mass ratio, at 180° angle of impingement, and no sonication.



Figure C.5.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water with a 3:1:1 drug-to-HPMC-to-SDS mass ratio, at 180° angle of impingement, and no sonication.


Figure C.5.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water with a 5:1:1 drug-to-HPMC-to-SDS mass ratio, at 180° angle of impingement, and 75 W of sonication.



Figure C.5.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water with a 3:1:1 drug-to-HPMC-to-SDS mass ratio, at 180° angle of impingement, and 75 W of sonication.



Figure C.5.5 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water with a 5:1:1 drug-to-HPMC-to-SDS mass ratio, at 180° angle of impingement, and 125 W of sonication.



Figure C.5.6 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water with a 3:1:1 drug-to-HPMC-to-SDS mass ratio, at 180° angle of impingement, and 125 W of sonication.



Figure C.5.7 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water with a 5:1:1 drug-to-HPMC-to-SDS mass ratio, at 180° angle of impingement, and 200 W of sonication.



Figure C.5.8 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water with a 3:1:1 drug-to-HPMC-to-SDS mass ratio, at 180° angle of impingement, and 200 W of sonication.



Figure C.5.9 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water with a 5:1:1 drug-to-HPMC-to-SDS mass ratio, at 180° angle of impingement, and 250 W of sonication.



Figure C.5.10 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by submerged impinging jets in mixture of HPMC, SDS and distilled water with a 3:1:1 drug-to-HPMC-to-SDS mass ratio, at 180° angle of impingement, and 250 W of sonication.

APPENDIX D

ADDITIONAL PARTICLE SIZE DISTRIBUTIONS AND SEM MICROGRAPHIC IMAGES FOR THE CONFINED IMPINGING JETS EXPERIMENTAL STUDY

Particle Size Distribution images from the Beckman-Coulter LS230 and SEM micrographic images for the Confined Impinging Jets Experimental Study are presented

in this Appendix as follows:

Additional experimental results of the effect of antisolvent-to- solvent mass flow ratio investigation at no sonication	D.1.1 – D.1.6
Additional experimental results of the effect of sonication power investigation at 3.32-to-1 antisolvent-to-solvent mass flow ratio	D.2.1 – D.2.4
Additional experimental results of the effect of sonication power investigation at 5.64-to-1 antisolvent-to-solvent mass flow ratio	D.3.1 – D.3.4
Additional experimental results of the effect of sonication power investigation at 8.11-to-1 antisolvent-to-solvent mass flow ratio	D.4.1 – D.4.4
Additional experimental results of the effect of sonication power investigation at 9.64-to-1 antisolvent-to-solvent mass flow ratio	D.5.1 – D.5.4
Additional experimental results of the effect of sonication power investigation at 11.01-to-1 antisolvent-to-solvent mass flow ratio	D.6.1 – D.6.4
Additional experimental results of the effect of sonication power investigation at 13.99-to-1 antisolvent-to-solvent mass flow ratio	D.7.1 – D.7.4

D.1 Additional Experimental Results of the Effect of Antisolvent-to-Solvent Mass Flow Ratio Investigation at No Sonication.



Figure D.1.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 3.32-to-1 antisolvent-to-solvent mass flow ratio, and no sonication.



Figure D.1.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 5.64-to-1 antisolvent-to-solvent mass flow ratio, and no sonication.



Figure D.1.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 8.11-to-1 antisolvent-to-solvent mass flow ratio, and no sonication.



Figure D.1.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 9.64-to-1 antisolvent-to-solvent mass flow ratio, and no sonication.



Figure D.1.5 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 11.01-to-1 antisolvent-to-solvent mass flow ratio, and no sonication.



Figure D.1.6 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 13.99-to-1 antisolvent-to-solvent mass flow ratio, and no sonication.





Figure D.2.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 3.32-to-1 antisolvent-to-solvent mass flow ratio, and 75 W of sonication.



Figure D.2.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 3.32-to-1 antisolvent-to-solvent mass flow ratio, and 125 W of sonication.



Figure D.2.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 3.32-to-1 antisolvent-to-solvent mass flow ratio, and 200 W of sonication.



Figure D.2.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 3.32-to-1 antisolvent-to-solvent mass flow ratio, and 250 W of sonication.

D.3 Additional Experimental Results of the Effect of Sonication Power Investigation at 5.64-to-1 Antisolvent-to-Solvent Mass Flow Ratio.



Figure D.3.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 5.64-to-1 antisolvent-to-solvent mass flow ratio, and 75 W of sonication.



Figure D.3.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 5.64-to-1 antisolvent-to-solvent mass flow ratio, and 125 W of sonication.



Figure D.3.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 5.64-to-1 antisolvent-to-solvent mass flow ratio, and 200 W of sonication.



Figure D.3.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 5.64-to-1 antisolvent-to-solvent mass flow ratio, and 250 W of sonication.

Differential Volume 5 4 3 -Volume (%) 2 1 0 -0.1 0.4 2 10 20 40 100 200 1000 0.04 4 1 Particle Diameter (µm) Mag = 9.72 K X EHT = 5.00 kV VVD = 8 mm EH7 = 5.00 kV WD = 8 mm Date :18 Aug 20 Time :22:28:41 Mag = 3.27 K X Signal A = RBSD Photo No. = 1410 Date :18 Aug 20 Time :22 26:23 Signal A = RBSD Photo No. = 1415

D.4 Additional Experimental Results of the Effect of Sonication Power Investigation at 8.11-to-1 Antisolvent-to-Solvent Mass Flow Ratio.

Figure D.4.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 8.11-to-1 antisolvent-to-solvent mass flow ratio, and 75 W of sonication.



Figure D.4.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 8.11-to-1 antisolvent-to-solvent mass flow ratio, and 125 W of sonication.



Figure D.4.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 8.11-to-1 antisolvent-to-solvent mass flow ratio, and 200 W of sonication.



Figure D.4.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 8.11-to-1 antisolvent-to-solvent mass flow ratio, and 250 W of sonication.

D.5 Additional Experimental Results of the Effect of Sonication Power Investigation at 9.64-to-1 Antisolvent-to-Solvent Mass Flow Ratio.



Figure D.5.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 9.64-to-1 antisolvent-to-solvent mass flow ratio, and 75 W of sonication.



Figure D.5.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 9.64-to-1 antisolvent-to-solvent mass flow ratio, and 125 W of sonication.



Figure D.5.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 9.64-to-1 antisolvent-to-solvent mass flow ratio, and 200 W of sonication.



Figure D.5.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 9.64-to-1 antisolvent-to-solvent mass flow ratio, and 250 W of sonication.



D.6 Additional Experimental Results of the Effect of Sonication Power Investigation at 11.01-to-1 Antisolvent-to-Solvent Mass Flow Ratio.

Figure D.6.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 11.01-to-1 antisolvent-to-solvent mass flow ratio, and 75 W of sonication.



Figure D.6.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 11.01-to-1 antisolvent-to-solvent mass flow ratio, and 125 W of sonication.



Figure D.6.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 11.01-to-1 antisolvent-to-solvent mass flow ratio, and 200 W of sonication.



Figure D.6.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 11.01-to-1 antisolvent-to-solvent mass flow ratio, and 250 W of sonication.

D.7 Additional Experimental Results of the Effect of Sonication Power Investigation at 13.99-to-1 Antisolvent-to-Solvent Mass Flow Ratio.



Figure D.7.1 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 13.99-to-1 antisolvent-to-solvent mass flow ratio, and 75 W of sonication.


Figure D.7.2 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 13.99-to-1 antisolvent-to-solvent mass flow ratio, and 125 W of sonication.



Figure D.7.3 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 13.99-to-1 antisolvent-to-solvent mass flow ratio, and 200 W of sonication.



Figure D.7.4 Particle size distribution and SEM micrographs of griseofulvin particles precipitated by confined impinging jets, at 13.99-to-1 antisolvent-to-solvent mass flow ratio, and 250 W of sonication.

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