Quantitative Approach between Secondary Nucleation and Mixing Hydrodynamics in Solution Crystallization System: Process Development and Scale-up

by

Mustafa Yousuf

Department of Mechanical, Aeronautical and Biomedical Engineering

University of Limerick

Ireland

Supervisor

Dr. Patrick J. Frawley

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Abstract

Crystallization via secondary nucleation allows the selective crystallization of a particular crystalline form which can lead to a more consistent crystalline product in terms of particle size distribution (PSD). Scaling up a crystallization process often results in significant changes to crystal size distribution (CSD), purity and morphology, which are key factors of product quality and has implications for downstream operations. The development of robust crystallization processes in which these parameters can be controlled requires a clear mechanistic understanding of nucleation. The convenient method to investigate this behavior is to determine the secondary nucleation threshold (SNT) of a crystallization system, which was found to be very sensitive to process variables such as mixing. Secondary nucleation and its qualitative relationship with agitation rate was a typical criterion used in the past. However, in the present work, a novel approach was established in which particle imaging velocimetry (PIV), a non-intrusive measurement technique, was used to quantify the mixing hydrodynamics with the cooling crystallization kinetics, as a function of fluid turbulent shear stress (TSS). All the crystallization experiments were performed in a solution crystallization of paracetamol in propan-2-ol solvent using a large single seed crystal of paracetamol which was held stationary in the agitating solution. Based on the experimental evidence, crystal nuclei breeding has been proposed as the mechanism of secondary nucleation in which pre-nucleated clusters from the solution nucleated at the interface of the seed crystal. These crystallites were weakly bound to the surface and readily sheared off by the fluid shear, which led to secondary nucleation. At a given scale, with the increased agitation rate, the SNT and product mean particle size were observed to decrease due to increased TSS. The increased TSS enhanced the rate of crystallites detachment from the seed surface, which facilitated the rate of secondary nucleation, and hence a decrease in SNT. From the results, secondary nucleation due to nuclei breeding was found to have a quantitative link with TSS which resulted in SNT to be independent of the scale under the influence of a constant TSS. This, in turn, leads to the production of a consistent PSD, independent of the scale. Moreover, the investigations revealed that using nuclei breeding approach in secondary nucleation, a controlled and uniform (narrow) PSD can be obtained in a given crystallization process through quantitative hydrodynamics. The novel approach established in the present work offers a potential for a more precise model in the process development and scale-up since nucleation is the direct consequence of nuclei breeding in which the fluid shear stress is the driving factor.
List of Publications


Declaration

This thesis is presented in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Limerick. No part of this thesis has been submitted for any academic award or part thereof at this or any other educational institution.

I declare that this research is my own effort other than the counsel of my supervisor. Where use has been made of the work of others, it has been acknowledged appropriately and fully referenced.

Signed: ________________________________ Date: ______________

Mustafa Yousuf
Dept. of Mechanical, Aeronautical & Biomedical Engineering,
University of Limerick, Ireland

Signed: ________________________________ Date: ______________

Dr. Patrick J. Frawley (Supervisor)
Dept. of Mechanical, Aeronautical & Biomedical Engineering,
University of Limerick, Ireland
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<td>$\bar{u}$</td>
<td>x-component of mean velocity</td>
<td>m sec$^{-1}$</td>
</tr>
<tr>
<td>$u_{tip}$</td>
<td>Impeller tip speed</td>
<td>m sec$^{-1}$</td>
</tr>
<tr>
<td>$V_m$</td>
<td>Molecular volume</td>
<td>m$^3$ molecule$^{-1}$</td>
</tr>
<tr>
<td>$\bar{v}'$</td>
<td>y-component of fluctuating velocity</td>
<td>m sec$^{-1}$</td>
</tr>
<tr>
<td>$Z$</td>
<td>Height of fixed crystal</td>
<td>mm</td>
</tr>
</tbody>
</table>

**Greek Letters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\varepsilon$</td>
<td>Specific power input</td>
<td>W kg$^{-1}$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Density of fluid</td>
<td>kg m$^{-3}$</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Turbulent shear stress</td>
<td>N m$^{-2}$</td>
</tr>
<tr>
<td>$\tau_{max,turb}$</td>
<td>Maximum turbulent shear stress</td>
<td>N m$^{-2}$</td>
</tr>
<tr>
<td>$\Delta G$</td>
<td>Gibb’s free energy of phase change</td>
<td>J molecule$^{-1}$</td>
</tr>
<tr>
<td>$\Delta G^*$</td>
<td>Energy barrier for nucleation from solution or</td>
<td>J molecule$^{-1}$</td>
</tr>
<tr>
<td></td>
<td>Maximum value of $\Delta G$ for critical radius</td>
<td></td>
</tr>
<tr>
<td>$\Delta \mu$</td>
<td>Supersaturation</td>
<td>J mol$^{-1}$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Chemical potential</td>
<td>J mol$^{-1}$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Dynamic viscosity</td>
<td>Pa s</td>
</tr>
<tr>
<td>$\theta$</td>
<td>Contact angle between a nucleus and substrate</td>
<td>°</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Relative supersaturation</td>
<td>-</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Interfacial free energy for homogenous primary nucleation</td>
<td>J m$^{-2}$</td>
</tr>
<tr>
<td>$\gamma_{eff}$</td>
<td>Interfacial free energy for heterogenous primary nucleation</td>
<td>J m$^{-2}$</td>
</tr>
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## Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>API</td>
<td>Active pharmaceutical ingredient</td>
</tr>
<tr>
<td>BVI</td>
<td>Bulk video imaging</td>
</tr>
<tr>
<td>CLD</td>
<td>Chord length distribution</td>
</tr>
<tr>
<td>CSD</td>
<td>Crystal size distribution</td>
</tr>
<tr>
<td>FBRM</td>
<td>Focused beam reflectance measurement</td>
</tr>
<tr>
<td>FFT</td>
<td>Fast-fourier transform</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transform infrared</td>
</tr>
<tr>
<td>GNZ</td>
<td>Growth only zone</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
</tr>
<tr>
<td>LDV</td>
<td>Laser doppler velocimetry</td>
</tr>
<tr>
<td>LIF</td>
<td>Laser-induced fluorescence</td>
</tr>
<tr>
<td>MSZ</td>
<td>Metastable zone</td>
</tr>
<tr>
<td>MSZL</td>
<td>Metastable zone limit</td>
</tr>
<tr>
<td>MSZW</td>
<td>Metastable zone width</td>
</tr>
<tr>
<td>PBT</td>
<td>Pitch blade turbine</td>
</tr>
<tr>
<td>PIV</td>
<td>Particle imaging velocimetry</td>
</tr>
<tr>
<td>PN</td>
<td>Primary nucleation</td>
</tr>
<tr>
<td>PSD</td>
<td>Particle size distribution</td>
</tr>
<tr>
<td>PTU</td>
<td>Programmable timing unit</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning electron microscopy</td>
</tr>
<tr>
<td>SN</td>
<td>Secondary nucleation</td>
</tr>
<tr>
<td>SNT</td>
<td>Secondary nucleation threshold</td>
</tr>
<tr>
<td>TDS</td>
<td>Turbulence dissipation rate</td>
</tr>
<tr>
<td>TSS</td>
<td>Turbulent shear stress</td>
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1. Introduction

1.1. Industrial Crystallization

Crystallization is a valuable technique which is widely used in the processing industry for separation and purification purposes. It involves multifaceted unit operations which can be challenging as a result of the interplay between chemical and physical aspects. The effectiveness of downstream processing and the quality of the crystalline product is highly influenced by the conditions prevailing during the crystallization process (Chen et al. 2011). The driving force in crystallization is the supersaturation under which two major conditions occur, i.e., crystal nucleation and growth (Lewis et al. 2015). In cooling crystallization, crystals form due to two distinct mechanisms: primary nucleation (PN) and secondary nucleation (SN), where secondary nucleation occurs at lower supersaturation due to the presence of parent crystals of the solute (Myerson 2002). Compared to primary nucleation, secondary nucleation allows the selective crystallization of a particular crystalline form (Lewis et al. 2015, Ulrich & Strege 2002), and as such; leads to a more consistent crystalline product in terms of particle size distribution (PSD).

In the pharmaceutical industry, crystallization is widely used to produce the active pharmaceutical ingredient (API) and the product quality strongly depends on the crystal size distribution (CSD), shape and purity. These parameters demand consistency in crystallization process from laboratory scale to production (Tung 2013). However, these conditions can be tailored by control over the nucleation
behaviour thus providing a way of modifying the product to the desired specification (Barrett et al. 2005). The convenient and often used method to investigate this behaviour is to determine the metastable zone width (MSZW) of a crystallization system. This is one of the most essential concepts and is widely used in industry and research to establish the strategies for a given crystallization system (Lewis et al. 2015, Ulrich & Strege 2002, Garside & Nyvlt 2002). However, in order to interpret the mechanism of a cooling crystallization system, the solubility of a given system must also be known. Solubility is a very important thermodynamic parameter which can also affect the kinetics of crystallization process, the particle size distribution and shape, which are controlled by the supersaturation (Tung 2013).

The MSZW of a system can be divided into two separate regions within the metastable zone of a solution crystallization: the growth only zone and the crystal proliferation zone. In other words, the boundary separating the growth only zone and the crystal proliferation zone can be termed as the secondary nucleation threshold (SNT) (Barrett et al. 2005). The width of the metastable zone can be defined as supercooling at which the first crystal appears when the solution is cooled from its saturation temperature ($T_S$) (Garside & Nyvlt 2002). It can also be determined by the difference between the saturation temperature of the solution, and the temperature at which the crystals are first detected (Threlfall & Coles 2016). The MSZW is an important characteristic of a crystallization system and strongly depends on different factors such as cooling rate, impurities, temperature, fluid dynamics and scale (Bogacz & Wójcik 2014, Kadam et al. 2011, Kim & Mersmann 2001, Ulrich & Strege 2002, Kubota 2008, Kashchiev & Borissova 2010, O'Grady et al. 2007, Ćosić et al. 2016). Interpreting the MSZW and SNT under different mixing conditions at the laboratory scale can be helpful in understanding the process operating window which provides considerable information for the likely performance of the crystallization process on scale-up.
1.2. Secondary Nucleation and Crystal Nuclei Breeding

Crystallization via secondary nucleation permits the selective crystallization of a specific crystalline form (Beckmann 2000, Lewis et al. 2015), and as such leads to a more consistent CSD, compared to primary nucleation. From the literature, several mechanisms were attributed to rationalize the origin of secondary nucleation. The first mechanism is attrition and includes mechanical micro-attrition due to mechanical breakage or attrition of crystals (Lewis et al. 2015, Beckmann 2000, Bendig & Larson 1976, Kadam et al. 2012, Mersmann 2001), in which attrition due to crystal-impeller collisions has been reported as the most likely mechanism for secondary nucleation (Kadam et al. 2012). The second mechanism is based on surface nucleation where the nuclei originate from clusters of solute molecules at the crystal-solute interface (Mersmann 2001).

Recently, crystal nuclei breeding has been proposed as a mechanism of secondary nucleation in which molecular aggregates from solution nucleate at the surface of a seed crystal (Anwar et al. 2015). These crystallites are then detached from the surface under the influence of the fluid shear which results in secondary nucleation. This was proposed to be an autocatalytic process in which the originated crystals can, in turn, serve as a seed. The nuclei breeding mechanism was further rationalized based on shadowgraphy experiments, where virtually no attrition or breakage of particles was observed due to particle-reactor wall interactions (De Souza et al. 2016). Seed crystals are typically suspended in an agitated system and, it therefore, becomes difficult to distinct nuclei breeding from attrition based secondary nucleation, particularly considering that seed crystals of large sizes could break. In a very recent work, a new approach was used to experimentally investigate the evidence of nuclei breeding using a single seed of paracetamol crystal, which was held stationary in the agitating solution (Yousuf & Frawley 2018). The results provided clear evidence of nuclei breeding as attrition enhanced secondary nucleation was not possible due to a stationary seed crystal. Furthermore, the experiments provided valuable information on the mixing hydrodynamics where the fluid shear stress was found to have a quantifiable impact on the secondary nucleation under the influence of agitation employed.
1.3. Mixing in Industrial Crystallization

Crystallization is generally performed in the stirred vessels through a mixing operation, which determines almost every aspect of the process involved (Paul et al. 2004, Adrian 1991). Stirred tanks typically generates complex flows under the action of rotating impellers and in a turbulently stirred tank, the flow structures are highly three-dimensional with high turbulence levels in the vicinity of the impeller. Therefore, understanding the fluid dynamic characteristics of the mixing flow in stirred tanks has remained a considerable interest of research over the years which often document power number, Reynolds number, and circulation times, characterizing the global flow field. However, there is an increasing demand for local flow information which is essential for robust design and scale-up (Hartmann et al. 2004).

The quality of mixing depends on several factors such as the agitating mechanism, design and location of the agitator, scale, hydrodynamics, and thermodynamics (Shimizu et al. 1998). Practically, agitated vessels are not always well mixed and the uniformity of mixing decreases as vessel size increases. Due to non-homogeneity in fluid flow, the velocity gradients are not homogeneously distributed in the vessel which results in a random shear stress distribution in different regions of the vessel. Therefore, poor mixing can promote concentration and temperature gradients within the vessel which in turn, results in different nucleation rates. The effect of the mixing on crystallization kinetics is multifaceted. It does not only influence the nucleation process, but it can also affect the mixing time, particle breakage, and crystal growth. The fluid dynamics of the stirring system, therefore, can hugely affect the MSZW which is a key parameter in controlling the quality of the crystallization process (Kadam et al. 2012). Although the geometrical configuration of the crystallizer has a significant effect on the product (CSD), this relationship has rarely been quantitatively linked with the system hydrodynamics (Celan et al. 2018). However, mixing conditions can be quantified using measuring techniques such as Laser Doppler Velocimetry (LDV) and Particle Imaging Velocimetry (PIV).
1.4. Particle Imaging Velocimetry

PIV has become very successful measurement technique in the domain of fluid dynamics with the rapid advancement of digital photography and the image analysis technique (Zhao et al. 2011). In the past, LDV was commonly used for such measurements, but this technique has its limitation in that it is a single point method to measure the flow characteristics. However, PIV can record all the velocity points of the flow field simultaneously. PIV is a non-intrusive measurement technique for quantifying fluid velocities (La Fontaine & Shepherd 1996), and highly capable of quantifying the properties of the turbulent flow. Turbulence in fluid flow occurs over a wide range of physical scales, from the largest scales of flow down to microscales or Kolmogorov scale. PIV is capable of measuring over such a wide dynamic range of scales in length with high accuracy for statistical analysis of turbulent flow (Adrian 2005).

Flow visualization is possible as the flow is seeded with small particles that are illuminated by a sheet of pulsed light and recorded using a high-speed camera. The essential principle of PIV is the measurement of the displacement of the particles over time, which is achieved through the cross-correlation method (Keane & Adrian 1992). In a cross-correlation technique, the displacement of the particles is measured by finding the maximum spatial cross-correlation between two interrogation regions over a known time which then produces a velocity vector (Keane & Adrian 1992, Adrian & Westerweel 2011). This process is performed repeatedly over the entire collection of images via a 2D Fast-Fourier Transform (FFT) (Adrian & Westerweel 2011, Keane & Adrian 1992, Raffel et al. 2018).

PIV has gained a considerable interest of research over the years due to its high capability and reliability in investigating the structure of the turbulent flow. However, the configuration of a PIV system can be time consuming and could lead to a high margin of error if the setup is not well arranged (Adrian 2005). For example, flow visualization around the objects can cause error in the data due to reflections. If the flow visualization is through transparent objects, then the laser light will refract and illuminate out-of-plane. However, this can be minimised by achieving the same refractive index of the mediums across the illuminated laser plane. The post-processing of the recorded images is a crucial step in determine the accuracy and
spatial resolution of the measurements; however, it is also the most time-consuming part of the entire process (Adrian & Westerweel 2011).

1.5. Scale-up in Industrial Crystallization

Scale-up is one of the most multifaceted operation of a crystallisation process which demands control over target quantities, such as particle size distribution, product yield and purity from batch to batch. The primary goal in scale-up is to provide a robust crystallization process from laboratory to production scale with minimum variability in the product quality. This complexity is of a major concern in pharmaceutical industry as only small amounts of APIs are usually available in early stages of development (Schmidt et al. 2004).

During scale-up, the physical effects of the crystallization process become significant for the success of an operation. This can significantly influence the CSD, purity, and morphology, due to the interlink between hydrodynamics and crystallization kinetics. These effects are the direct consequence of mixing concepts such as power per unit volume, particles suspension, shear rate, and heat transfer (Schmidt et al. 2004). For the effective execution of the scale-up rules based on different mixing concepts, the geometrical similarity between the crystallisation configurations must be ensured.

To predict the performance of a batch cooling crystallisation on scale-up, the kinetics of the given crystallisation process should be determined to quantify any potential impact on product yield. These kinetic parameters are crystal growth and nucleation to predict PSD (Mullin & Nyvlt 2001, Zhou & Kovenklioglu 2004, Monnier et al. 1997). Understanding and optimising the crystallization process window can be helpful to minimize any potential downstream handling problems. It also highlights the impact of critical process variables on the product quality and yield, hence providing a potential opportunity to improve the manufacturing process.
1.6. Research Objectives

Nucleation is a decisive step in crystallization which can significantly affect the product quality and downstream operations. The development of robust crystallization process in which the product crystal size distribution (CSD) and polymorphic outcome can be controlled involves a clear understanding of nucleation which, in turn, is highly sensitive to the mixing conditions. Mixing in industrial crystallization is generally performed in a mechanically agitated stirred tank and its link with crystallization kinetics under the influence of agitation rate has remained a challenge in process scale-up since the problem has been tackled mainly by means of semi-empirical methods. Secondly, crystallization via secondary nucleation is commonly employed in industrial crystallization. However, seed crystals are typically suspended in agitated systems which may lead to difficulties in controlling secondary nucleation due to attrition enhanced nucleation. Considering that seed crystals of large sizes could break, particularly at higher agitating speeds, this can lead to unfavorable outcomes such as fine generations. Therefore, to tackle these problems, this research proposes a new approach in the industrial crystallization process development and scale-up, which was quantitatively linked with the mixing hydrodynamics. The key goal of the research is to control the crystallization operating window of a given system across different scales by controlling the secondary nucleation. This was accomplished through a quantitative approach in which SNT was linked to mixing hydrodynamics as a function of turbulent shear stress. Particle imaging velocimetry (PIV), a robust and non-intrusive quantitative measurement technique, was used to determine these shear stresses by measuring the instantaneous velocity field in the region of interest (seed surface) during mixing. The second major goal is to have a better understanding and control over PSD in scale-up through controlled secondary nucleation. To meet this requirement, a novel approach was adopted in cooling crystallization experiments. Crystallization was performed using a large single seed crystal which was held stationary in agitating systems. This resulted in a uniform particle size distribution which was found to be consistent, irrespective of the scale. This is a robust approach to perform crystallization via secondary nucleation since the attrition enhanced nucleation was not possible compared to more traditional approaches where the seeds are used in bulk and prone to breakage. This can result in a wider particle size distribution which is not desirable in industrial processes.
1.7. Thesis Outline

The rest of the chapters are:

Chapter 2: The crystallization process has been discussed in detail, including some important aspects such as solubility, supersaturation, nucleation kinetics, metastable zone width, secondary nucleation threshold and particle size distribution measurements.

Chapter 3: This chapter provides a background on particle imaging velocimetry as a quantitative measurement technique, including its working principle and significance in mixing.

Chapter 4: In this chapter, the overall research methodology has been highlighted which is mainly divided into two sections; particle imaging velocimetry and cooling crystallization experiments.

Chapter 5: The core of this thesis lies in the concept of crystal nuclei breeding as a mechanism of secondary nucleation. This mechanism has been outlined in this chapter, which also provides an experimental evidence of crystal nuclei breeding based on a laboratory scale experimentation.

Chapter 6: This chapter is based on laboratory scale experiments which were performed to investigate the impact of turbulent fluid shear stress in mixing on secondary nucleation via crystal nuclei breeding. The turbulent shear stress was determined at different agitation rates using particle imaging velocimetry.

Chapter 7: In this chapter, fluid turbulent shear stress has been investigated using PIV as a function of scale-up of cooling crystallization experiments. The experiments evidently revealed the quantitative impact of shear stress in mixing, which resulted in a controlled PSD, irrespective of scale.

Chapter 8: This chapter is extended from the previous chapters, i.e. chapter 6 and 7, where the concept of controlled secondary nucleation under the influence of turbulent shear stress in mixing has been extended to the industrial crystallizers.
Chapter 1: Introduction

1.8. References


Chapter 1: Introduction


2. Crystallization and Fundamentals

Crystallization is an extremely old unit operation which is still used in the production of highly specialised fine chemicals and pharmaceutical products. In early civilizations, crystallization was used in the production of salt in coastal areas using large open ponds. Today crystalline products can be found in every aspect of life, such as salt, sugar and chocolate, as shown in Figure 2.1. These products have relevant product characteristics which are determined by their specific crystal properties tailored via crystallization. Therefore, prediction of the crystal size distribution (CSD) is a key focus in the field of industrial crystallization.

Crystallization is an imperative separation and purification technique in the production of final or intermediate industrial products. Crystallization occurs due to a phase transformation in which a crystalline material is obtained from a solution. The product form and quality are associated with the crystal size distribution of the crystals, crystal shape, inclusion of impurities in crystal, the degree of agglomeration and the surface roughness of crystal. These product properties are analogous to the selected mode of crystallization process and type of hardware used for production, since crystallization process is governed by thermodynamics of phase transition, mass and heat transfer, fluid flow and reaction kinetics (Lewis et al. 2015).
Crystallisation is a valuable and frequently applied process in the manufacture of active pharmaceutical ingredients (APIs). It is used as a primary means of intermediate or final product formation to achieve a desired purity and form (Schmidt et al. 2004). In the pharmaceutical industry, the need of better control is reinforced to satisfy the regulatory authorities so that a continuing supply of APIs of high and reproducible quality can be delivered (Tung 2013). These requirements demand efficacy of the crystallization process to meet time and supply constraints, scalability from laboratory to production, and robustness throughout all phases of drug development. In the pharmaceutical industry, the product quality is strongly influenced by the particle size distribution (PSD) and shape which can also have a detrimental impact on downstream unit operations such as the filtration, drying and formulation operations (Barrett et al. 2005, Jones et al. 1987, De Souza et al. 2016). Therefore, control over crystal size and shape is regarded as an important research and development goal (De Souza et al. 2016). In the pharmaceutical sector, the
development of a new drug typically takes over 10 years and requires drug substance and products in sufficient quantities for testing and approval (Wei 2010). Consequently, it is particularly important to get manufacturing decisions right as early as possible, since changing the manufacturing route is very difficult once the Food and Drug Administration (FDA) approval is obtained (Wei 2010).

In the crystallization process, nucleation is the commencement of a new phase, which plays a decisive role in determining the crystal shape and size distribution. Thus, understanding the fundamentals of nucleation is crucial to the control of crystallization processes (Chen et al. 2011).
2.1. Solution Crystallization

The crystallization method is principally based on the solubility of the crystalizing compound. In general, crystallization can be categorised into two main methods, i.e., melt crystallization and solution crystallization. A melt generally refers to a multi-component homogenous liquid mixture that solidifies upon cooling (Lewis et al. 2015). This method is applied if the solute solubility is very high and when the product purity must be extremely high. In so
crystallisation, a phase transformation results in a solid crystalline product of an ordered structure from a homogeneous solution (Myerson 2002). For crystallization from solution, the solubility of the solute is generally moderate or low. Crystallization by solution is a commonly employed method in the manufacturing of fine chemicals, food and pharmaceutical products. Crystallization from solution can be further distinguished into four different methods which are as follows;

- Cooling crystallization
- Evaporative crystallization
- Precipitation
- Anti-solvent crystallization.

The work presented in this research is entirely based on cooling crystallization processes; therefore, other methods are not discussed further. Cooling crystallisation involves the cooling of a solution which results in an increase in the supersaturation to the point that nucleation occurs with the formation of crystallized material. In cooling crystallization, the saturation concentration or solute solubility is highly sensitive with change in temperature. Therefore, determining the solubility and metastable zone width (MSZW) is the first and foremost step in the development of a cooling crystallization system. The MSZW indicates the concentration at which spontaneous nucleation occurs due to an increase in the supersaturation. The supersaturation can significantly affect the product CSD by controlling the rate of nucleation and growth. Therefore, solubility and supersaturation are the major control variables for cooling crystallization processes. Shown in Figure 2.2 is a typical CSD of a paracetamol API, produced in a solution crystallization of paracetamol.
Figure 2.2. Scanning electron microscope (SEM) image of paracetamol product crystal formed by cooling crystallisation process. (De Souza et al. 2016)
2.2. Solubility

As crystallization is related to the phase change in solid-liquid systems, the analysis of a crystallization process starts with the consideration of phase diagram. Phase diagrams display all the possible thermodynamic states of a system. For crystallization from solution, it is usual to represent the phase equilibrium information in terms of solubility curves, as shown in Figure 2.3. Solubility can be defined as the amount of a solute that can be dissolved in a specific amount of solvent at a given temperature (Tavare 1995). It can also be defined as the amount of solute required to obtain a saturated solution under given conditions. The accurate solubility data of bioactive compounds is of critical importance to the pharmaceutical industry, not only in terms of quantifying drug absorption and bioavailability, but also essential for the development of manufacturing operations (De Souza et al. 2017). The solubility of paracetamol in different solvents is presented in Figure 2.4. In the presented research, which involves solution crystallization of paracetamol in propan-2-ol, the solubility data is taken from the same literature.

Figure 2.3. Solubility curve from the nitrate-water system. (Lewis et al. 2015)
Figure 2.4. Solubility of paracetamol in each of the alcohols as determined using (○) published literature values, (▲) pressurized-synthetic data, and (□) the extended gravimetric data set. (De Souza et al. 2017)
2.3. **Supersaturation.**

The concept of supersaturation formation in a solution is the first step in the crystallization process. A supersaturated solution contains a higher amount of dissolved solute than it would normally contain in a saturated solution at a given temperature. The evolution of the particle size distribution (PSD) is often determined by the competitive balance between the crystal growth and nucleation, which is highly influenced by the level of supersaturation. The degree of supersaturation is an important factor because it is the driving force of a crystallization process (Myerson 2002). Figure 2.5 is a phase diagram which illustrates different regions of a phase equilibrium system. The solution is said to be undersaturated (subsaturated), if the thermodynamic state of the solution is below the solubility line. If the solution is at the solubility line, it is called saturated and if it is above the solubility line, the solution is supersaturated. In order to properly characterise the degree of these processes, quantitative variables are required. In reaction kinetics, the true driving force is the chemical potential (Lewis et al. 2015). In a thermodynamic equilibrium of a multi-phase system, the chemical potential of each component is equal through all the phases and thus, can be expressed as

\[ \mu_{\text{liquid,eq}} = \mu_{\text{solid}} \]  

(2.1)

Where \( \mu_{\text{liquid,eq}} \) and \( \mu_{\text{solid}} \) represents the chemical potential of the crystallizing compound in a solution and as a solid, respectively.

If the system equilibrium is disturbed, for example; cooling, the solution becomes supersaturated. The chemical potential of the solute in solution \( \mu_{\text{liquid}} \) is now higher than the corresponding equilibrium value \( \mu_{\text{liquid,eq}} \). The difference between the chemical potential of the solute in the supersaturated and saturated states is called supersaturation and represents as,

\[ \Delta \mu = \mu_{\text{liquid}} - \mu_{\text{liquid,eq}} = \mu_{\text{liquid}} - \mu_{\text{solid}} \]  

(2.2)
The relative supersaturation and supersaturation ratio are alternative and commonly used expressions for the degree of supersaturation. These are defined by equation 2.3 and 2.4 respectively.

\[
\sigma = \frac{\Delta C}{C_{eq}} \quad (2.3)
\]

\[
S = \frac{C}{C_{eq}} \quad (2.4)
\]

Where \( \Delta C = C - C_{eq} \)

In this thesis (chapter 6, 7 and 8), the supersaturation ratio has been termed as *relative supersaturation ratio* and denoted as \( S_r \).

**Figure 2.5.** Diagram showing the critical degree of supersaturation and the different stability states of supersaturated systems. (Parhi & Swain 2018)
2.4. Nucleation.

Crystallization from solution is accompanied by a two-step process. The first step is the formation of new crystals and the second is their growth to observable sizes (Tavare 1995). Therefore, a complete understanding of the crystallization process requires knowledge of both nucleation and crystal growth, in which supersaturation is the driving force. Nucleation occurs due to the formation of new crystallites, which is mainly attributed under two broad mechanisms, i.e., primary or secondary. In primary nucleation, crystals are formed from a clear solution under the influence of high supersaturation. In secondary nucleation, new crystals are generated at a low or moderate supersaturation due to the presence of the seed crystals or parent crystals of the solute. These two mechanisms are then further subdivided, as illustrated in Figure 2.6. In the following section, the mathematical expressions used to define the rate of nucleation, for primary and secondary nucleation, has been referenced from Lewis et al (2015).

Figure 2.6. Classification of nucleation mechanisms. (Myerson 2002)
Primary nucleation can be divided into homogeneous and heterogeneous, which are discussed using mathematical models to express respective nucleation rates.

### 2.4.1. Homogenous Primary Nucleation

If the phase transition takes place due to local fluctuations of the concentration in the clear (free from foreign particles or impurities) solution, it is called homogeneous primary nucleation. According to the classical theory of nucleation (Volmer 1939, Nielsen 1964), nucleation occurs as a result of statistical fluctuations of solute entities clustering together in the solution. In a saturated solution, the system of cluster formation and decay is in equilibrium and the solution is stable against new phase formation. In a supersaturated solution, however, clusters of critical size are formed that either fall apart or become stable nuclei that grow further. The rate of nucleus formation by this mechanism is given by an Arrhenius type of expression, i.e., equation 2.5.

\[
J = AS \exp \left[-\frac{\Delta G^*}{kT}\right]
\]

(2.5)

Where \( J \) is the rate of nucleation and \( AS \) is the pre-exponential factor. \( A \) has a theoretical value of \( 10^{30} \) nuclei/m\(^3\) s. \( S \) is often taken as 1 since its change has a minor influence in pre-exponential factor.

Crystallization is a phase transition for which the free energy change is the sum of the free energy change for the formation of the nucleus surface and the free energy change for the phase transformation. This is the thermodynamic consideration of homogenous nucleation (Nielsen 1964, Gibbs 1928). The Gibbs free energy as a function of cluster radius is illustrated in Figure 2.7, which can be expressed by equations 2.6. and 2.7.

\[
\Delta G = \Delta G_{volume} + \Delta G_{surface}
\]

(2.6)
\[ \Delta G = -\frac{k_v L^3}{V_m} \Delta \mu + k_a L^2 \gamma \]  

(2.7)

Where \( L \) is the size of the cluster and \( k_a \) and \( k_v \) are surface and volume shape factors.

\( \gamma \) is interfacial free energy [J m\(^{-2}\)]

\( V_m \) is molecular volume [m\(^3\) molecule\(^{-1}\)]
The small clusters are approximated as spheres, which results in

$$\Delta G = -\frac{4\pi r^3}{3V_m} \Delta \mu + 4\pi r^2 \gamma$$  \hspace{1cm} (2.8)$$

Where \( r \) is the radius of the cluster in [m].

The Gibbs free energy is maximum at a certain critical size of the nucleus. Clusters below this nucleus size will eventually decay, and beyond this size will grow further to become stable nuclei. This critical cluster radius can be found by minimizing the free energy equation with respect to the radius, i.e., \( \frac{d(\Delta G)}{dr} \), thus equation 2.8 becomes

$$r^* = \frac{2\gamma V_m}{\Delta \mu}$$  \hspace{1cm} (2.9)$$

The corresponding critical Gibbs free energy is then

$$\Delta G^* = \frac{4}{3} \pi r^{*2} \gamma$$  \hspace{1cm} (2.10)$$

Using \( \Delta \mu = kT \ln S \) in equation 2.9 and then substituting in 2.10, the critical Gibbs free energy becomes

$$\Delta G^* = \frac{16\pi \gamma^3 V_m^2}{3k^2 T^2 (\ln S)^2}$$  \hspace{1cm} (2.11)$$

Where \( S \) is supersaturation ratio.
Substituting eq 2.11 in 2.5, the nucleation rate now can be expressed as

\[
J = AS \exp \left[ - \frac{16\pi \gamma^3 v_m^2}{3kT^3 (\ln S)^2} \right]
\]  
(2.12)

**2.4.2. Heterogenous Primary Nucleation**

Usually, primary nucleation is facilitated by the presence of an interface in the solution. This invisible or microscopic particle such as dust or dirt particle, on which nucleation preferentially starts, is called heterogenous primary nucleation. A foreign substance present in a supersaturated solution reduces the energy required for nucleation. Therefore, nucleation in a heterogeneous system generally occurs at a lower supersaturation than in a homogeneous system. The decrease in free energy depends on the contact (or wetting) angle of the solid phase (Volmer 1939), as shown in Figure 2.8. Therefore, for heterogenous nucleation, the free energy is

\[
\Delta G_{hetero}^* = \varphi \Delta G_{homo}^*
\]  
(2.13)

with \( 0 \leq \varphi \leq 1 \)
Figure 2.8. Nucleation on a foreign substrate. (Kashchiev 2000)

For complete wetting ($\theta = 0^\circ$) $\varphi = 0$

For $\theta = 90^\circ$ the value of $\varphi = 0.5$

By replacing $\varphi \gamma^3$ in equation 2.12 by $\gamma_{eff}^3$, the following expression is obtained for heterogeneous nucleation rate.

$$J_{hetero} = A_{hetero} S \exp \left[ -\frac{16\pi \gamma_{eff}^3 V_m^2}{3k^3T^5(\ln S)^2} \right]$$ (2.14)
2.4.3. **Secondary Nucleation.**

In the supersaturated solution, the presence of one or more crystals of the material being crystallized can induce nucleation. This type of nucleation is called secondary nucleation. The seed crystals consume the supersaturation, which is too low to induce primary nucleation, but still allow secondary nuclei to grow in the crystal population. These parent crystals have a catalytic effect on the nucleation phenomena, and hence, secondary nucleation occurs at a lower supersaturation compared to primary nucleation.

The rate of secondary nucleation in a suspension of growing crystals can be expressed by an empirical power law that contains three experimental parameters. These parameters are the growth rate $G$, the rotational speed $N$ and the mass of solid content $M_T$. Thus, it can be expressed as

$$B_0 = k_N G^i N^h M_T^j$$  \hspace{1cm} (2.15)

Where $B_0$ is the rate of secondary nucleation in $[m^3 s^{-1}]$.

$G$ is directly related to the relative supersaturation $\sigma$ defined by equation 2.16.

$$G = k_g \sigma^g$$ \hspace{1cm} (2.16)

And $\sigma$ is related to the specific power input $P_0$

The power law is also given by equation 2.17.

$$B_0 = k_N^1 \sigma^b P_0^k M_T^j$$ \hspace{1cm} (2.17)
Where $i = b/g$ and $h = 3k$

$1 \leq b \leq 3$ and $0.6 \leq k \leq 0.7$

For secondary nucleation dominated by crystal-impeller collision, $j = 1$
For secondary nucleation dominated by crystal-crystal collision, $j = 2$

### 2.4.4. Mechanisms of Secondary Nucleation.

Following are the different mechanisms of secondary nucleation, named after their origin.

*Initial breeding or dust breeding* usually occurs when dry seed crystals are introduced into a solution. During storage or dry handling, small fragments are formed by attrition that stick to the dry seeds. When these seeds are introduced in the solution, tiny crystallites are formed on the surface of the crystal which are then washed away in the solution and become new nuclei. Therefore, it is recommended to wash away these fragments by suspending the seeds in a slightly undersaturated solution before feeding as a slurry to the crystallizer.

In *polycrystalline breeding*, at a very high supersaturation, irregular polycrystalline aggregates can also be formed that are prone to fragmentation. Fragments of these polycrystals can, in turn, serve as secondary nuclei. Therefore, these mechanisms only occur at high supersaturations which can have an unfavourable effect on the crystal quality.

At high stirring speeds, *macroabrasion* (also called collision or attrition breeding) of crystals results in fragments that serve as nucleation sites. As opposed to contact nucleation, this phenomenon results in the rounding of edges and corners of crystals. The rate of nucleation by this mechanism is a function of the crystal hardness, the concentration of the suspension, and the retention time.
Dendritic breeding results due to surface instabilities that occur during outgrowth of the crystals under a high supersaturation. This happens when the corners and the edges of the crystal experience a higher supersaturation than the middle surface. Thus, these protruding sides/surfaces easily break off and fragment in the solution, and eventually serve as nucleation sites.

Fluid shear breeding occurs under the action of fluid shear stress on the surface of the seed crystal, hence, resulting in the formation of attrition enhanced fragments. However, a very high shear stress is needed to exceed the yield stress of a parent crystal to form these fragments which can then serve as secondary nuclei.

Contact nucleation is considered as the most important source of secondary nucleation which results from collisions between crystals and impeller, crystals and vessel wall and collisions between the crystals. In contact nucleation, secondary nuclei are generated either by microabrasion or from the absorbed layer of the solute that has not yet crystallized.

Recently, crystal nuclei breeding has been proposed as a mechanism of secondary nucleation (Anwar et al. 2015). In crystal nuclei breeding, the pre-existing clusters or molecular aggregates in the solution, by coming in contact, nucleate to form crystallites at the interface of the seed surface. These crystallites are then sheared off by the action of the fluid shear. As the crystallites are detached, the surface is free to repeat the process. This is a catalytic process in which the newly formed crystals can, in turn, serve as seeds. This whole phenomenon is illustrated in Figure 2.9.

The core of the present research involves secondary nucleation based on crystal nuclei breeding mechanism, which has been discussed thoroughly in chapter 5 and throughout this thesis.
Figure 2.9. Snapshots from molecular dynamics simulations of a crystal slab (representing the seed crystal) immersed in a supersaturated solution of solute, illustrating the three supersaturation regimes: a) Starting configuration. b) Low supersaturation. c) Moderate supersaturation. d) High supersaturation. (Anwar et al. 2015)
2.5. MSZW and SNT

In solution crystallisation, a solute will remain in a solution until a high level of required supersaturation is generated to induce spontaneous nucleation. The extent of this supersaturation at which primary nucleation occurs is called metastable zone width (MSZW) (Myerson 2002). It can also be defined as the difference between the saturation temperature (solubility temperature) and the temperature at which the crystals are first detected (Bogacz & Wójcik 2014). MSZW can be influenced by a variety of process parameters including solubility, rate of supersaturation generation, impurity inclusion, mixing, and solution history (Barrett et al. 2005). It is therefore important to characterize MSZW under a specific set of operating conditions, which relate closely to the conditions of the final scale crystallization (Barrett & Glennon 2002). The development of robust crystallization processes requires a clear mechanistic understanding of nucleation. The convenient and often used method for determining this behaviour is to interpret the MSZW of a given crystallization system (Nyvlt et al. 1970, Omar & Ulrich 2006, Ulrich & Strege 2002). The polythermal method is the most widely used approach for determining the MSZW (Barrett et al. 2005, Garside & Nyvlt 2002, Kadam et al. 2011), in which a saturated solution is cooled at a constant cooling rate until nucleation occurs. This phenomenon is illustrated in Figure 2.10. A solution of concentration C₂ with the saturation temperature of T₂ (point B) is initially cooled from a higher temperature (point A). The cooling continues at a constant rate until the solution reaches the temperature T₁ and nucleation occurs. This temperature is the nucleation temperature at which the first crystals are detected in the solution (point C). The MSZW can eventually be determined by measuring the difference between the temperatures, i.e., T₂ – T₁.

Numerous techniques have been utilised to determine the MSZW of a crystallization process, including FBRM, turbidity, ultrasound velocity, electrical conductivity, in situ video probes, bulk video imaging, IR spectroscopy and red diode lasers (Barrett & Glennon 2002, Mitchell et al. 2011, Yousuf & Frawley 2018). These different techniques can also have influence on the measurements of MSZW (Mullin & Jancic 1979). The method of detection can have a noticeable impact on the success of the system kinetics due to time lag following nucleation as the crystals grow to a detectable size range (Mitchell & Frawley 2010, Nagy et al. 2008). The mixing
hydrodynamics have a significant influence on the nucleation kinetics of a given crystallization system. Therefore, MSZW can be affected and observed to decrease with increasing agitation levels (Yousuf & Frawley 2018, Liang et al. 2004). This has been discussed in detail in chapter 6 and 7.

In the crystallization process of a given system, different mechanisms of nucleation have different metastable zone limits where secondary nucleation has the smallest limit, followed by primary heterogeneous and largest for primary homogeneous (Lewis et al. 2015, Ulrich & Strege 2002, Kubota 2008). This is clearly illustrated in Figure 2.11.

The metastable zone between the solubility curve and the crystallisation curve (MSZW) can be divided into two regions, growth only zone and crystal proliferation zone (Threlfall & Coles 2016). The region that separates these two regions is defined as the secondary nucleation threshold (SNT). In other words, SNT is the limit at which secondary nucleation occurs as the solution is cooled from its saturation temperature in the presence of the seed crystal or crystals. This can be interpreted from Figure 2.12. At a supersaturation less than that of the secondary nucleation threshold the seeds will only grow but not proliferate. This is defined as the seed growth only zone of a

Figure 2.10. Determination of the maximum supercooling ΔT, in the polythermal method of MSZW. (Bogacz & Wójcik 2014)
crystallization system. In this figure, a dead zone boundary is also shown near the solubility curve. This is the limit in the MSZW within which even a seeded solution is incapable of either crystal growth or crystal proliferation zone. The interpretation of these regions, particularly the SNT and MSZW, can be very helpful in characterising the crystallization process window of a given system.

**Figure 2.11.** MSZW for different nucleation mechanisms. (Mitchell 2012)

**Figure 2.12.** The generalized solution crystallization diagram, indicating, MSZW (green line), SNT (red line) and solubility curve (blue line). (Threlfall & Coles 2016)
2.6. Particle Size Distribution

The crystal size distribution of a crystalline product is an important criterion for assessing the properties and quality of a product. Normally, a crystalline product does not consist of single-sized crystals but consists of a wide distribution of sizes instead (Myerson 2002). There are several mathematical models that can be used for describing the PSD produced by industrial crystallizers. Generally, the “particle size” is used to denote the mean size of the crystals, however, several other terms have been used, such as the median size (Allen 1990). In the pharmaceutical industry, the properties of APIs such as purity, stability, rate of absorption and bioavailability are strongly affected by their particle sizes that comprise the powder or dispersion. A typical PSD of a crystallized paracetamol (API), measured on volume-based method, is shown in Figure 2.13.

![Volume based PSD of paracetamol measured through laser diffraction](De Souza et al. 2016)

Particle size measurement is routinely carried out across a wide range of chemical industries, including pharmaceutical. The main reason to employ particle characterization is to have a better control of product quality by developing an understanding of how particle properties can affect the final product and downstream processing. Particle size is an important physical property of particulate samples which can be critical to the success of many manufacturing businesses. A particle can be
defined as a discrete sub-portion of a substance. In order to simplify the measurement process, it is often convenient to define the particle size by the diameter of an equivalent sphere having the same property (such as volume or mass) as the actual particle (Malvern Instruments 2017), as shown in Figure 2.14. This perception works very well for regular shaped particles. However, it may not always be appropriate for irregularly-shaped particles, as illustrated in Figure 2.15. For a rod-shaped particle, a volume equivalent sphere would give a particle diameter of 198 µm, which is not a very accurate description of its true dimensions. However, the particle can also be defined as a cylinder with the same volume which has a length of 360 µm and a width of 120 µm.

Figure 2.14. Illustration of the concept of equivalent spheres. (Levoguer 2012)

Figure 2.15. Illustration of the volume equivalent rod and sphere-shaped particles. (Levoguer 2012)
2.6.1. Weighing Methods in Particle Size Distribution

A particle size distribution can be represented in different ways with respect to the weighing of individual particles which ultimately depends on the measuring principle being used. In practice, the two main methods which are commonly used are number weighed and volume weighed distributions. In number-based method, each particle is given equal weighing irrespective of its size. This is most often useful when knowing the absolute number of particles is important. In the other method, the contribution of each particle in the distribution relates to the volume of that particle (equivalent to mass if the density is uniform), i.e., the relative contribution will be proportional to size (Allen 1990). This is often extremely useful from a commercial perspective as the distribution represents the composition of the sample in terms of its volume/mass (Levoguer 2012). In the pharmaceutical industry, particle size measurement on volume-based distribution is preferred for most applications. (Burgess et al. 2004)

As an example, shown in Figure 2.16, three particles are 1 µm, three are 2 µm, and three are 3 µm in size. Based on number distribution, these particles will generate the result shown in Figure 2.17 (a), where each particle size accounts for one third of the total. However, if the analysis is based on a volume distribution, the result would be totally different as shown in Figure 2.17 (b). In volume distribution analysis, 75% of the total volume comes from the 3 µm particles, and less than 3% comes from the 1 µm particles. Therefore, when presenting as a volume distribution it becomes obvious that most of the total particle mass or volume comes from large size particles.


**Figure 2.16.** Particles 1, 2 and 3 μm in size. (HORIBA Scientific 2012)

**Figure 2.17.** Distribution of the particles. (a) Number distribution, (b) Volume distribution. (HORIBA Scientific 2012)
2.6.2. Laser Diffraction: A Volume-Based Analysis

Currently, the most widely used technique for PSD determination is laser light scattering based on a laser diffraction principle, which is widely used for materials ranging from hundreds of nanometres up to several millimetres in size. Laser diffraction results are mainly reported on a volume basis. Therefore, the volume mean can be used to define the central point although the median is more frequently used when using this technique (Particle Sciences 2009). Laser diffraction measures particle size distributions by measuring the angular variation in the intensity of light scattered as a laser beam passes through a dispersed particulate sample. Large particles scatter light at small angles relative to the laser beam and small particles scatter light at large angles, as illustrated in Figure 2.18. The angular scattering intensity data is then analysed to calculate the size of the particles responsible for creating the scattering pattern, using the Mie theory of light scattering (Malvern Instruments 2017). These results are then transformed into a particle size distribution (Allen 1990, Malvern Instruments 2017, HORIBA Scientific 2012, Particle Sciences 2009). In laser diffraction, the particle size is reported on “equivalent spherical diameter”, i.e., the diameter of a sphere of equivalent volume (Particle Sciences 2009, Barth 1984).

![Figure 2.18. Scattering of light from small and large particles. (Malvern Instruments 2017)](image-url)
2.6.3. Interpretation of a Particle Size Distribution

The interpretation of particle size distribution can be presented with different statistical parameters but the choice of the most appropriate parameter for a given sample depends on how that data will be used and with what it will be compared. These statistical parameters are mean, median and mode, as presented in a non-symmetrical distribution in Figure 2.19. For a symmetric distribution, all central values are equivalent (HORIBA Scientific 2012), i.e., mean = median = mode

“Mean” is defined as the average size of the particles in a sample or the arithmetic mean of the area under the PSD curve. The modal value is that size where most particles are located.

“Median” is defined as the size in the middle of a frequency distribution. The median is a value at which 50% of the particles are greater and 50% smaller.

“Mode” is defined as the size with highest frequency. Or the peak of the frequency distribution. It may be easier to visualize it as the highest peak in the distribution. However, the mode is not as commonly used, but can be descriptive.

Figure 2.19. Illustration of the median, mode and mean for a particle size. (Malvern Instruments 2017)
2.6.3.1. Mean

Mean can be further defined in different ways because the mean value is associated with the basis of the distribution calculation. The three most commonly used for particle sizing are based on number, surface and volume, as illustrated in Figure 2.20.

- **Number length mean: D[1,0]**

  It is often referred to as the arithmetic mean and is most important when the number of particles is of interest.

- **Surface area moment mean: D[3, 2]**

  The surface area mean (Sauter Mean Diameter) is relevant when the specific surface area is important e.g. bioavailability, reactivity, dissolution. It is most sensitive to the presence of fine particulates in the size distribution.

- **Volume moment mean: D[4, 3]**

  The volume moment mean (De Brouckere Mean Diameter) is most relevant for many samples as it accounts the size of the particles which constitute the majority of the sample volume. However, it is very sensitive to the presence of large particulates in the size distribution.

![Figure 2.20](image.png)

**Figure 2.20.** Illustration of the D[4,3] and D[3,2] on a particle size distribution where a significant proportion of fines are present. (Malvern Instruments 2017)
2.6.3.2. Median

Median can also be defined in three different ways based on number (Dn50), surface (Ds50) and volume (Dv50) statistics. The Dv50 is the median of a volume distribution. Similarly, Dn50 and Ds50 are used as medians for number and surface distributions respectively. Since the primary result from laser diffraction is a volume distribution, it is a common practice to express laser diffraction results as Dv10, Dv50, and Dv90 values. As illustrated in Figure 2.21, the Dv50, the volume median, is defined as the diameter (size) where half of the population lies below this value. Similarly, Dv90 reflects the size which lies below the 90% in the distribution, and Dv10 represents the population that lies below the 10%. These values are very convenient statistics to understand and meaningful for describing particle size distributions (HORIBA Scientific 2012). These terms, based on volume distribution, are also expressed as D10, D50, and D90 without including the term v.

Figure 2.21. Illustration of the Dv10, Dv50 and Dv90 on a typical particle size distribution where a significant proportion of fines are present. (Malvern Instruments 2017)
Given that some specifications are based on a mean diameter, i.e., “average size”, this approach can be complicated by the fact that there are several mean values that can be calculated and reported in the result (Levoguer 2012, Barth 1984, HORIBA Scientific TN156). The most common mean value noted when using laser diffraction is the volume mean, or D[4,3], which is very sensitive to the presence of large particles in the distribution. The median is the most stable calculation generated by laser diffraction and should be the value used for a single point specification in most cases. The more common practice is to include two points which describe the coarsest and finest parts of the distribution. A three-point specification featuring the Dv10, Dv50, and Dv90 will be considered complete and appropriate for most particulate materials (HORIBA Scientific 2012, Particle Sciences 2009).

In the present thesis, all the measurements related to the particle size distribution are volume-based distribution analysed through laser diffraction principle. The particle size analyser (instrument) used is the Malvern Mastersizer 3000 which works on a laser diffraction principle. This method has been discussed in section 2.6.2. Further detail on the sampling technique of a crystallized material to measured PSD through Mastersizer 3000 is discussed in section 6.1.4, and a same procedure was adopted for all the PSD measurements in this research work. All the results are presented in terms of mean particle size, which are discussed in the respective chapters, i.e., chapter 6, 7 and 8.
2.7. References


Chapter 2: Crystallization and Fundamentals


Volmer, M. *Kinetik der Phasenbildung*; Steinkoff, Dresden, Germany 1939.

Chapter 3: Particle Imaging Velocimetry

3. Particle Imaging Velocimetry

Many technical and scientific developments require a measuring technique that can measure the velocity distribution across an extended area of a flow field. This can be achieved by scanning a point velocity probe across the flow, but the instantaneous structure is lost and only the average flow field is obtained (LaVision 2014). Flow visualization techniques can often reveal instantaneous flow structure but are only qualitative or semi-quantitative at best (Adrian & Westerweel 2011). An optical, non-intrusive method that is related to both flow visualization and optical point techniques has developed over the last 20 years called particle imaging velocimetry (PIV). This technique can provide an accurate quantitative measure of the instantaneous flow field velocity across a planar area of a flow field. PIV is a measurement technique that was actually developed to measure wall bounded turbulent flows (Adrian 2005).
3.1. How PIV Works

PIV comprises a class of flow measuring techniques that are characterized by the recording of the displacement of small particles embedded in a region of a fluid. The principle behind a PIV system is very straightforward. The flow is illuminated by a light source, and the particle positions are recorded on a recording medium such as a photographic film. The recorded particle displacement field is measured locally across the whole field of view, which is then divided by the known pulse separation to obtain flow velocity at each point. In general, the favourable arrangement of a 2D PIV system is that the biggest velocity component of the observed flow field is parallel to the light sheet while camera viewing direction is normal (Raffel et al. 2018). This arrangement is shown in Figure 3.1.

![PIV System Diagram](Image)

**Figure 3.1.** General setup of a 2D PIV system. (LaVision 2014)

PIV has become an important tool for quantitative and instantaneous measurement of laboratory flows. The principle methodology of a PIV system typically consists of several subsystems (Raffel et al. 2018). This mainly comprises of experimental setup, seeding the flow, illumination of the flow, recording the images, calibration, evaluation and postprocessing. Generally, in most applications, tracer particles have to be added to the flow. An example of a typical PIV flow visualization is illustrated in Figure 3.2. The flow is seeded with tiny, neutrally buoyant particles
(tracers). Using a light sheet, formed by passing a double pulsed laser beam through an optical arrangement, the particles in the flow are illuminated twice with a small-time separation between. A camera positioned perpendicular to the plane of the light sheet is shuttered to capture the light scattered from the particles in the plane of flow. The light scattered by the particles are recorded either on a single frame or on a sequence of frames. Depending on the flow velocity and the factor of magnification of the camera lens, the delay of the two pulses are selected such that adequate displacements of the particle images can be obtained. From the time delay between the two illuminations and displacement of the tracers, velocity vectors can be calculated. The velocity vector field generated from this system is shown in Figure 3.3.

![Figure 3.2. Typical setup of a 2D PIV system for flow visualization. (LaVision 2014)](image1)

![Figure 3.3. Velocity vector field evaluated through PIV. (LaVision 2014)](image2)
3.2. PIV Evaluation Techniques

For the evaluation of the particle images it is assumed that the tracers or seeds follow the flow into the local flow velocity between the two illuminations (Adrian 1991). The digital PIV recording is divided in small subareas called interrogation windows. Using statistical correlation techniques, one local displacement vector is determined for each interrogation window (Adrian & Westerweel 2011). For this reason, the size of this interrogation cell is selected such that all particles within this area have moved homogeneously in the same direction and the same distance. For good results, the number of particles within one interrogation cell should be at least 7 to 10 (Keane & Adrian 1992). The evaluation of the particle images depends on the way these images have been recorded by the camera. One way is to record the scattered light of both illuminations in one frame, i.e., single frame/double exposure. These images can be evaluated by auto-correlation. The other and often use method is to record the scattered light from the first illumination in one frame and the second illumination in another frame. This is called double frame/double exposure. These double frame images can be evaluated by cross-correlation. Both these methods are discussed below (Adrian & Westerweel 2011, LaVision 2014).

**Auto-Correlation.** In this method, the scattered light from first and second exposure of the particles is recorded in one image. The complete image is subdivided in small areas called interrogation windows and each window is evaluated by auto-correlation. The auto-correlation function is characterised by two identical correlation peaks rotationally symmetrical about the highest central peak indicating zero displacement, as shown in Figure 3.4. In consequence, one cannot detect the sign of the displacement because it is not clear which particle is illuminated by the first and the second laser pulse. Therefore, the information from the auto-correlation is ambiguous and not conclusive if some prior information about the observed flow is not known. Moreover, the detection of very small displacements can be a problem when the correlation peaks are very close to the central peak. Compared to cross-correlation, the auto correlation peak is significantly smaller and high noise increases the possibility that the displacement correlation peak disappears in the background.
Cross-Correlation. In this method, the scattered light from first and second exposure of the particles is recorded in two different images. A complete image is subdivided in interrogation windows which are evaluated by cross-correlation. For cross-correlation, a fast-double shuttered CCD camera is typically used to record images with double frame/double exposures. The minimum time delay between the two laser pulses is limited by the time necessary for the frame transfer of the camera. Compared to the auto-correlation, a higher and explicit correlation peak is formed in cross correlation, as shown in Figure 3.5.
3.3. PIV in Mixing

Stirred-tank reactors, mechanically agitated by one or more impellers, are among the most widely used reactors in chemical and allied industries. The rotation of impellers generates extremely complex flow within the stirred vessel. The inconsistencies in mixing quality can be attributed to the lack of a clear understanding of the mixing processes due to the complex nature of impeller-induced turbulence in agitated vessels (Raju et al. 2005). Therefore, understanding fluid dynamic characteristics of the impeller discharge flow is essential for reliable design and scale-up of stirred reactors (Wang et al. 2006). The distributions of velocity, turbulent kinetic energy and kinetic energy dissipation are of importance for the design, optimization, and scale-up of agitated vessels. In particular, the local energy dissipation rate is a key element in controlling micro-mixing (Xinhong et al. 2008).

In the past, the main technique available for measuring fluid flow has been Laser Doppler Velocimetry (Dyster et al. 1993, Geisler et al. 1994, Lusseyran et al. 1994, Ng et al. 1998). However, LDV has its limitation in that it is a single point technique to measure the flow characteristics (Raffel et al. 2018, Suzukawa et al. 2006). PIV is a non-intrusive and efficient technique capable of measuring the whole flow field instantaneously. PIV measures all the velocity points of the flow field at a time and is highly capable of quantifying the properties of a turbulent flow (Adrian & Westerweel 2011).

In last two decades, a noteworthy research has been devoted investigating the structure of fluid flow in the stirred tank reactors using PIV. Mostly involved investigations are velocity profiles, fluctuating velocities, Reynolds stresses, turbulent kinetic energy and turbulent dissipation rate. Some examples are briefly discussed here. Jian et al. (1998) used PIV to investigate the instantaneous velocity flow field along the central axial plane of a stirred vessel with a P-4 axial impeller to study mean velocity field, turbulent kinetic energy, turbulence dissipation rate and Reynolds stresses. Escudié and Liné (2003) used PIV to determine the mean flow field, the turbulent fluctuations and turbulence characteristics produced by a Rushton turbine. Myers et al. (1997) reported flow field instabilities of axial-flow impellers using PIV. Aubin et al. (2004) studied the hydrodynamics of the liquid phase in an aerated vessel stirred with a six pitched blade turbine (PBT) using PIV measurements. Sharp and
Adrian (2001) used PIV to study the small-scale flow structure and turbulent kinetic energy dissipation around a Rushton turbine in a stirred tank. Baldi and Yianneskis (2004) obtained mean velocities, Reynolds stresses and turbulent kinetic energy dissipation from fluctuating velocity gradient measurements with 2-D and 3-D PIV in a Rushton turbine stirred tank.

Driss et al. (2014) conducted PIV experiments in a baffled vessel stirred by Rushton impeller to investigate the effect of Reynolds number on the time averaged velocity field. Figure 3.6 presents the time-averaged velocity field between two blades over 170 image pairs of instantaneous velocity fields for impeller speed varying over Reynolds numbers ranging from 17000 to 58000. According to these results, the Reynolds number has a direct effect on the intensifying values of the velocity field and the impeller generates two main vertical motions, above and below the impeller region.

Figure 3.6. Velocity vector map. (Driss et al. 2014)
In another work (Xinhong et al. 2008), PIV was used to study the turbulent characteristics in a vessel agitated by dual Rushton turbine. The distributions of the kinetic energy dissipation for merging flow at six angles have been evaluated as shown in Figure 3.7. It visualizes that the high dissipation rate is located in the vortex region. A range of fluctuations, in the vortex region, include large scales that are generating turbulent kinetic energy and the smallest scales where the turbulence is dissipated.

**Figure 3.7.** Angle-resolved turbulent kinetic energy dissipations of merging flow at different angles. (Xinhong et al. 2008)
3.4. Fluid Shear Stress

The fluid flow causes friction due to viscosity, which is the primary source of shear stress in the fluids. At any given plane of a fluid particle there are three forces acting on the fluid particle, as shown in Figure 3.8, one normal and two shear stresses. First subscript refers to the direction of force and second subscript to direction of perpendicular to the plane. In 3D, the stresses experienced by a fluid element can be arranged as a $3 \times 3$ matrix also known as the stress tensor. The stress tensor is symmetric and depends on only six independent components: three normal stresses ($\sigma_{xx}, \sigma_{yy}, \sigma_{zz}$) and three shear stresses ($\tau_{xy} = \tau_{yx}, \tau_{xz} = \tau_{zx}, \tau_{yz} = \tau_{zy}$).

**Figure 3.8.** Stresses on the faces of a fluid element. (Corona et al. 2016)

Stress Tensor:

$$\tau = \begin{bmatrix} \sigma_{xx} & \tau_{xy} & \tau_{xz} \\ \tau_{yx} & \sigma_{yy} & \tau_{yz} \\ \tau_{zx} & \tau_{zy} & \sigma_{zz} \end{bmatrix}$$
Chapter 3: Particle Imaging Velocimetry

3.5. Characteristics of Turbulence in Mixing

The fundamental difference between laminar and turbulent flow lies in the chaotic, random behaviour of the various fluid parameters. Such variations occur in the three components of velocity, the pressure, the shear stress, the temperature, and any other variable that has a field description (Munson et al. 2013). For a detailed description of the turbulent fluid flow in stirred vessels, it is of primary interest to determine both the circulation flow and the local specific turbulent energy dissipation rate (Mersmann & Geisler 1991).

**Fluid Velocity:**

For the description of the different fluid flows in turbulent agitated vessels, it is necessary to determine the local fluid velocities. For local isotropic turbulent fluid flows (Munson et al. 2013), the fluid velocity can be defined as

\[ u(t) = \bar{u} + u' \]  \hspace{1cm} (3.1)

Where \( u(t) \) is the local velocity (\( x \) component of instantaneous velocity), \( \bar{u} \) is its mean value and \( u' \) is fluctuating component of the local velocity. The maximum value of the local velocity characterises the bulk fluid circulation in the entire vessel and for turbulent flow \( Re > 10000 \), the local fluid velocity can be normalized by the stirrer tip speed (Mersmann & Geisler 1991), which is defined as

\[ u_{tip} = \pi ND \]  \hspace{1cm} (3.2)

**Energy Dissipation Rate:**

For local isotropic turbulence the local energy dissipation rate can be calculated by the effective value of the turbulent fluctuating velocity \( u' \) and impeller diameter \( D \) (Mersmann & Geisler 1991), as given in equation 3.3.
\[
\varepsilon = C \frac{u'^3}{D} \tag{3.3}
\]

Where \( C \) is a constant = 5/7 but should be regarded for a more detailed description as a function of the impeller and the vessel geometry ratio.

In stirred vessels it is of great interest to determine the maximum value of the local normalized energy dissipation rates, i.e., \( \frac{\varepsilon}{\bar{\varepsilon}} \) \( \text{max} \), which depends on the turbulent power number \( P_{0_{\text{turb}}} \) and the D/T ratio. This relation is given in equation 3.4.

\[
\left[ \frac{\varepsilon}{\bar{\varepsilon}} \right]_{\text{max}} = 0.14 C P_{0_{\text{turb}}}^{1/3} \left[ \frac{D}{T} \right]^{-3} \left[ \frac{H}{T} \right] \tag{3.4}
\]

**Turbulent Shear Stress:**

Turbulent fluid flows can be characterized by large local and time depending changes of the fluid velocity. This leads to an additional amount of shear stress, called turbulent or Reynold shear stress. The total shear can be regarded as (Corona et al. 2016, Mersmann & Geisler 1991, Munson et al. 2013).

\[
\tau = \tau_{\text{lam}} + \tau_{\text{turb}} \tag{3.5}
\]

This is also given by

\[
\tau = \mu \frac{d\bar{u}}{dy} + \rho \bar{u}' \bar{v}' \tag{3.6}
\]

The amount \( \tau_{\text{lam}} \) depends on the dynamic viscosity \( \mu \) which is dominating in the vicinity of the vessel walls. The quantity of the turbulent shear stress within a local isotropic turbulent fluid flow \( \tau_{\text{turb}} \) is prevailing in the bulk fluid flow and can be
expressed as a function of the fluid velocity $\rho$ and effective turbulent fluctuating velocities (Mersmann & Geisler 1991, Munson et al. 2013).

$$\tau_{turb} = \rho \overline{u' \nu'}$$ (3.7)

The amount of $\tau_{lam}$ can be neglected for turbulent fluid flows because it is much smaller than the amount of $\tau_{turb}$. In the following equation, the turbulent shear stress is based on the dynamic pressure which originates from fluid density $\rho$ and the stirrer tip speed.

$$\frac{\tau_{turb}}{\rho u_{tip}^2} = \left[ \frac{4P_{turb}}{\pi^4 C} \right]^{2/3} \left[ \frac{D}{T} \right] \left[ \frac{H}{T} \right] \left[ \frac{\varepsilon}{\bar{\varepsilon}} \right]^{2/3}$$ (3.8)

The above equation is valid for turbulent fluid flows, corresponding to $Re > 10000$. The maximum values of $\frac{\tau_{turb}}{\rho u_{tip}^2}$ are always located in the discharge region of the impellers. This relation can be defined in a more simplified form (Mersmann 2001) and given as

$$\frac{\tau_{max,turb}}{\rho (N\pi D)^2} \approx \left( \frac{P_{turb}}{2\pi^4} \right)^{2/3} \frac{D H}{T T} \frac{\varepsilon}{\bar{\varepsilon}}^{2/3}$$ (3.9)

This equation has been used as reference for the determination of maximum turbulent shear stress in the vicinity of the impeller, as discussed in chapter 8. For a turbulent flow, $\frac{\varepsilon}{\bar{\varepsilon}} = 1$ and $P_{turb}$ is constant as function of $D/T$ ratio.
3.6. References


Chapter 3: Particle Imaging Velocimetry


4. Research Methodology

The development of robust crystallization process involves a clear understanding of mixing hydrodynamics which can significantly influence the nucleation and growth kinetics of a given crystallization system. In the present work, particle imaging velocimetry (PIV) was used to determine the fluid turbulent shear stress (TSS) in mixing as a function of cooling crystallization experiments, which were performed in two different agitating systems, i.e., magnetically stirred vessels and mechanically agitated stirred tank reactors. The work presented involves systematic experiments which were performed in SSPC research laboratories at University of Limerick. The research methodology is mainly divided into two parts, i.e., particle imaging velocimetry and cooling crystallization. First, PIV was used for the measurement of the fluid turbulent shear stress (TSS) at each agitation rate employed. Subsequently, cooling crystallization experiments were performed for the determination of secondary nucleation threshold as a function of TSS. All the crystallization experiments were performed in a solution crystallization of paracetamol in propan-2-ol solvent using a large single seed crystal of paracetamol which was held stationary in the agitating solution.

This chapter outlines an overall methodology that has been adopted to carry out these experiments, including experimental setups and equipments. However, the individual details on the complete procedure are further discussed in the following chapters, i.e., 6, 7 and 8.
4.1. Cooling Crystallization Experiments

4.1.1. Magnetically Stirred Vessels.

A schematic overview of a crystallization setup is shown in Figure 4.1. A 100 ml borosilicate vessel containing 70 ml saturated solution was completely submerged in a transparent polycarbonate bath filled with deionized water to enable visualization. In these experiments, a TX150 thermostat was programmed using LabWise 2.1.2 software to control the temperature of the water bath in combination with a C2G immersion cooler. A MIXdrive 15 magnetic stirring plate was used for stirring in combination with a Teflon coated magnetic stirrer. The stirring rate was controlled using a MIXcontrol 20. The onset of nucleation was detected using an MRL-III-635L-30Mw red diode laser which was calibrated to detect particles as small as 20 nm. A G400 FBRM probe was used for the real-time tracking of the particle chord length distribution. A real image of this arrangement is shown in Figure 4.2.

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Figure 4.1. Experimental illustration. (1) Laser power supply, (2) MRL-III-635L-30Mw laser, (3) Polycarbonate water bath, (4) TX150 thermostat, (5) G400 FBRM probe, (6) C2G Immersion cooler, (7) 100 ml vessel with a seeded crystal in 70 ml propan-2-ol solution, (8) MIXdrive 15, (9) Laser detector, (10) Computer.
Figure 4.2. A real image of a crystallization setup.

In this system, cooling crystallization experiments were performed in a solution volume of 70, 120, 580 and 1000 ml scales using laboratory scale borosilicate glass vessels of 100, 500 and 1000 ml sizes, as shown in Figure 4.3. The geometric details of these vessels along with scale-up configuration are discussed in chapter 7, section 7.1. The stirring operation was performed using Teflon coated magnetic stirrer bars of diameter 35, 55 and 64 mm which are shown in Figure 4.4.

Figure 4.3. Borosilicate vessels of 100, 500 and 1000 ml.
The experiments performed required the stationary suspension of a seed crystal in the stirring solution. To serve the purpose, crystal holders were designed using 316L stainless-steel, which were experimentally tested to ensure it would not provide enhanced sites for heterogeneous nucleation during a crystallization run. This procedure is discussed in section 5.1 for the current setup. These crystal holders are shown in Figure 4.5. They were designed to fit the borosilicate vessels as shown in Figure 4.6. The seed crystals used are discussed in the next chapter, section 5.1.

Initially, different methods were adopted to test the suitability of the experiments in which the seed crystal was suspended directly using a cotton thread or a nylon cap tied with a cotton thread. However, these methods failed due to enhanced heterogenous nucleation sites.
Figure 4.6. A 100 ml borosilicate vessel containing 316 stainless-steel crystal holder with a paracetamol seed crystal.

The detection for the onset nucleation was performed with an MRL-III-635L-30Mw laser, as shown in Figure 4.7. These lasers are commonly used for Optogenetics, fluorescence excitation, microscopy, flow cytometry, material sciences, machine vision, laser display and a broad spectrum of other applications. As shown in Figure 4.8, the laser illuminates a focused beam of red light passing through the solution and the presence of particles was detected by the decrease in the transmission of light, measured by the laser detector. The wavelength of this laser is $635 \text{ nm}$ with an output power of 30 mW. A laser detector measured the intensity of laser power once focused on its lens. The detection of nucleation using laser method was found to be reliable for these experiments, however, the minimum size of the particle that could be detected by the laser was not known. Therefore, an experiment was performed to calibrate the laser and to estimate the minimum size of the particle that could be detected. The test was performed based on the laser diffraction principle, using 20 nm particles of silicon oxide. This procedure is discussed in detail in section 6.1.2.
Chapter 4: Research Methodology

Figure 4.7. MRL-III-635L-30Mw laser unit for the detection of nucleation.

Figure 4.8. MRL-III-635L-30Mw laser beam passing through the solution during crystallization process.
Chapter 4: Research Methodology

The in-situ FBRM used is a METTLER TOLEDO G400 probe, as shown in Figure 4.9, which was primarily used for the real-time tracking of the particle counts. It is a probe-based instrument that is inserted directly into laboratory vessels or reactors to track changing particle size and count in real time. The FBRM works on backscattered light signal analysis. The suspended particles in the solution backscattered the focused beam of laser light which is then detected by the probe. For all FBRM measurements, a measurement frequency of 1 sec was employed with a scan speed of 2 m/sec. G400 FBRM has a measurement range of 0.5 - 2000 µm.

![METTLER TOLEDO G400 probe](image)

**Figure 4.9.** METTLER TOLEDO G400 probe.

In these experiments, Grant Optima™ TX150 thermostat (Figure 4.10) was used to control the temperature of the water bath in combination with an immersion cooler. The thermostat is a high-performance programmable digital heating circulator which allows fast set-up of multiple parameters and provides sophisticated control for temperature-controlled applications in the range of -50 to 150 °C. The unit includes a heater for fast heat-up, a powerful integral pump for circulating temperature-controlled fluid around external apparatus. The cooling control was performed using Grant C2G refrigerated immersion cooler as shown in Figure 4.11. The refrigerated immersion cooler consists of a cooling coil connected to a refrigeration unit by a flexible pipe. The system offers a continuous heat extraction, with the bath control unit controlling the temperature. This unit is compatible with TX150 thermostat used.
Figure 4.10. Grant Optima™ TX150 thermostat.

Figure 4.11. Grant C2G refrigerated immersion cooler.
4.1.2. Mechanically Agitated Stirred Tank Reactors.

This section summarizes the methodology related to cooling crystallization experiments which were performed in 1000 and 5000 ml mechanically agitated reactors. In these experiments, cooling crystallization in a solution volume of 1 L was performed in METTLER-TOLEDO OptiMax™ 1001 thermostat system. For 5 L scale, Syrris-Orb double jacketed reactor system was used. The onset of nucleation at both scales were detected using in-situ G400 FBRM probe and the solution concentration was scrutinized using in-line FTIR spectroscopy. As discussed in the previous section, these experiments were performed utilizing a same approach where a single seed crystal of paracetamol was held fixed in the agitating reactors with the aid of specifically designed 316L stainless-steel crystal holder. The general setup of a crystallizer is shown in Figure 4.12.

![Figure 4.12. Schematic of a crystallizer setup in cooling crystallization.](image)

(1) Borosilicate vessel, (2) Temperature probe, (3) IR probe, (4) Overhead stirrer gear, (5) FBRM probe, (6) 316L stainless-steel crystal holder, (7) Paracetamol seed crystal, (8) Four-blade, 45° pitch-blade turbine impeller.
Figure 4.13 shows Optimax 1001 thermostat system which was used for cooling crystallization experiments in 1 L reactor (vessel). This is a powerful solid-state thermostat which provides necessary heating and cooling to control the temperature of the reactor synthesis accurately and precisely. In Optimax thermostat, experiments are controlled using an intuitive touchscreen system where experimental parameters can be adjusted rapidly, and a sequence of tasks can be programmed simultaneously. Optimax 1001 thermostat can precisely operate over a temperature range from -40 to 180 °C. This system can also be programmed using PC software iControl™ which can be used to interpret and import comprehensive set of data. The reactor system used for 5 L reactor is shown in Figure 4.14. This is a compact bench-top jacketed reactor system and can be operated over a wide range of temperatures, between -90 °C and 250 °C. This system has a similar touch control system which also operates using the same iControl™ software.

Figure 4.13. METTLER-TOLEDO OptiMax™ 1001 thermostat system.
The reactors (vessels) used in these experiments are shown in Figure 4.15. These vessels have a standard configuration that comes with the respective reactor systems. The geometric details of these reactors along with their scale-up configuration are given in the experimental section of chapter 8, section 8.1. Both the reactors were made of borosilicate glass with torispherical bottom, which were mechanically agitated using a four-blade, 45° pitch blade turbine. The impeller diameter for 1 L reactor is 41.5 mm whereas for 5 L reactor, the impeller diameter is 70 mm. These impellers are PTFE coated and shown in Figure 4.16.
Figure 4.15. 1 and 5 L borosilicate glass vessels with torispherical bottom.

Figure 4.16. PTFE coated four-blade, 45° pitch blade turbine for 1 and 5 L reactors.
In this system, the crystal holders for the suspension of seed crystal are shown in Figure 4.17. The crystal holders were made of 316L stainless-steel which were also tested for the feasibility of crystallization experiments. This procedure is outlined in chapter 8, section 8.1.2.

![Figure 4.17. 316L stainless steel crystal holders for 1 and 5 L reactors.](image)

In these experiments, the concentration of the solution during the course of crystallization was monitored using METTLER TOLEDO ReactIR 15 system as shown in Figure 4.18. ReactIR 15 is a real-time, in situ mid-infrared based system to study reaction kinetics. ReactIR 15 can be programmed using a PC based software, i.e., iC IR™, which provides a graphical way to describe the characteristics of a chemical reaction and optimize chemistry. For all the IR experiments, a measurement frequency of 1 minute was selected.

The detection of nucleation and measurement of particles total count was scrutinized using METTLER TOLEDO G400 FBRM, which is mentioned in the previous section.
Figure 4.18. METTLER TOLEDO ReactIR 15.
4.2. Particle Imaging Velocimetry

As discussed previously, cooling crystallization experiments were performed in two different agitating systems as a function of fluid turbulent shear stress. It was necessary to determine these shear stresses in both the systems separately that could be linked with the crystallization kinetics. However, irrespective of the agitating system involved, the essential methodology of a PIV measurement is the same. This mainly comprises of seeding the flow with homogeneously distributed particles, illumination of the seeded flow using double pulsed laser sheet with a short-time delay between them and recording the images using a high-speed camera positioned perpendicular to the plane of the light sheet. The PIV system used is LaVision commercially available PIV system, which was used for all the experiments. The system comprises of Nd:YAG double pulsed laser, v1211 high-speed camera and a programmable timing unit. Therefore, a combined methodology for both the agitating systems is discussed in this section. However, the experimental setup of an individual system is outlined clearly. The experimental procedure of PIV measurement for each agitating system is further detailed in the respective chapters, i.e., chapter 6, 7 and 8.

The experimental setup of a PIV measurement in magnetically stirred vessels is illustrated in Figure 4.19. This setup has been replicated from the cooling crystallization experiments (Figure 4.1). For mechanically agitated system, the experimental illustration is provided in Figure 4.20.

**Figure 4.19.** Experimental illustration of PIV setup in magnetically stirred vessel. (1) Computer, (2) PTU, (3) Nd:YAG double pulsed laser, (4) Polycarbonate transparent bath, (5) v1211 high-speed camera, (6) Vessel with propan-2-ol solution and 316L holder, (7) MIXdrive 15, (8) 150 x 150 x 5 mm Perspex sheet.
Figure 4.20. Experimental illustration of PIV setup in mechanically stirred tank reactor. (1) Computer, (2) PTU, (3) Nd:YAG double pulsed laser, (4) Perspex box containing 1 L reactor, (5) v1211 high-speed camera.

PIV measures the entire velocity vector fields by tracking the motion of particles in bulk while taking two high-resolution images at a small-time difference of $\mu$s. As shown in the arrangements of Figure 4.19 and 4.20, these velocity profiles were captured using a laser sheet plane illuminated by a 10,000 Hz laser with 10.6 W and a wavelength of 532 nm (Nd:YAG laser). This is a shuttered continuous wave (CW) laser which is shown in Figure 4.21. A VC-Phantom v1211 high-speed camera, as shown in Figure 4.22, was directed at a 90° angle to the illuminated plane to capture the images. Utilising a widescreen CMOS sensor, the v1211 camera can acquire 12 Gigapixels/second of data at full megapixel resolution of 1280 x 800, and over 12,000 frames/second. Both the laser and the high-speed camera were connected to a computer via LaVision’s universal synchronizer and a timing unit, i.e., programmable timing unit (PTU). PTU is the hub of all intelligent imaging systems which generates precise trigger pulses for cameras, lasers and other external devices under the control of DaVis software. This PTU is shown in Figure 4.23. For all the experiments performed, regardless of the system, the flow was seeded with 20 $\mu$m polyamide particles. Figure 4.24 shows a PIV experiment for 5 L reactor setup which was
illuminated in the laser sheet. The vessels used in PIV experiments are the same which were used in the crystallization experiments, as shown in Figure 4.3 and 4.15.

Figure 4.21 Nd:YAG Shuttered CW laser.

Figure 4.22 VC-Phantom v1211 high-speed camera.
Figure 4.23. LaVision programmable timing unit (PTU).

Figure 4.24. 5 L reactor illuminated by Nd:YAG Shuttered CW laser.
4.3. **PIV Calibration**

The goal of PIV is to measure the velocity vector field in the fluid at a given section or plane of interest. PIV accomplishes this by taking two high resolution images sequentially and calculates the distances travelled between groups of particles over a known time. If the acquired images are distorted the images need a correction based on spatial calibration. This can include distortions due to the curvature of the vessel since the laser sheet can reflect or refract, if the medium through which the laser sheet passes has a different refractive index. To minimize the effect of such optical distortions between camera and flow, the medium refractive indexes should be similar or nearly the same. In these experiments, the whole vessel was submerged in a square tank made of perspex glass, which was filled with clean water to minimize the distortion of the laser sheet through the optical arrangement. Ideally, the square tank should be filled with propan-2-ol, since this was the actual fluid in the mixing vessel under investigation. However, under health and safety regulations, and due to serious hazards associated with propan-2-ol it was not safe to use it as a filling medium in perspex box. Therefore, water as the filling medium served the purpose as the refractive index of the water and propan-2-ol is 1.33 and 1.37 respectively. Moreover, the refractive index of perspex is 1.49 and borosilicate glass is 1.51, which was well enough to keep the laser sheet refraction to minimal.

Before recording any images, calibration of the camera must be done in the laser sheet field of view in order to get the correct and quantifiable results. The calibration is usually performed through a calibration dialogue in Davis software using a suitable calibration plate. The calibration plates used in this work are shown in Figure 4.25. A large (left most calibration plate in the image) calibration plate was used for 5 L vessel. The centre calibration plate was used for 1 L vessels in both agitating systems, i.e., magnetically stirred and mechanically stirred vessels. The smallest calibration plate was only used for 100 and 500 ml magnetically stirred vessels. All the calibration plates were 4 mm thick 3D printed and had an array of small black dots spaced 10 mm apart. All the plates have round dots (marks) 1 mm in depth and 2.5 mm in diameter. For a particular agitating system and vessel size, as mentioned above, a calibration plate was placed horizontally in the field of view. The camera positioned perpendicular to the field of view captured the image of the calibration plate. The
calibration wizard generates the calibration in eight steps. Among them, marking and mapping are the most important steps. In marking function, after an image is taken, first three starting marks are defined based on the selected coordinate system in 2D. Then using the “Start Search” dialog button, the software automatically finds other marks based on a polynomial fit algorithm. Once all the marks are detected, fit mapping function is used to start the calibration using “Start Calibration” dialog button. The calibration process is automatic and based on fit mapping function, fit parameters are calculated, i.e., the average deviation of mark. A fit parameter value lower than 1 pixel is good and lower than 0.3 pixel is excellent. A value higher than 2 pixels is dubious. For all the PIV experiments in this research, calibration was successfully performed for all the systems with average deviation to mark value being found to be around 0.154, which is considered as an excellent calibration result.

Figure 4.25. 3D printed PIV calibration plates of sizes 200 mm (left most), 143 mm (centre) and 95 mm (right most).
5. Crystal Nuclei Breeding

Secondary nucleation by means of seed crystals is extensively employed in the crystallization process and remained a noteworthy consideration of research over the years, but still many aspects of its mechanism have yet to be elucidated (Cui & Myerson 2014). Two distinct mechanisms are broadly attributed to the origin of secondary nucleation i.e., crystal attrition and crystal nuclei breeding.

Crystal nuclei breeding is the mechanism in which pre-clusters from solution nucleate at the surface of primary seed crystal. This process has been revealed based on a molecular dynamic simulation, which is illustrated in Figure 5.1. It was proposed that the nucleated crystallites are weakly bound to the seed surface which are then detached from the surface under the influence of the fluid shear which results in secondary nucleation. This is an autocatalytic process in which the originated crystals can, in turn, serve as a seed and repeat the process.
In this work, a novel approach was adopted to further rationalize the mechanism of crystal nuclei breeding based on a laboratory scale experimentation under cooling crystallization. A large single seed crystal of paracetamol was used in a propan-2-ol solution, which was held stationary in a magnetically stirred vessel with the aid of a specifically designed 316L stainless steel holder to prevent it from attrition or breakage during the agitation process.
5.1. Materials and Seed Crystal Preparation

The seed crystal of paracetamol which is used in the investigation is shown in Figure 5.2. It was initially prepared via cooling crystallization of a high supersaturated solution \( S_0 = 2.0 \) at a saturation temperature \( T_S \) of 30 °C, using paracetamol solute in propan-2-ol solvent. The solute used was a commercially available, monoclinic form of paracetamol (acetaminophen, 99.9% pure), which was also used for the preparation of a solution. A 100 ml solution was prepared by dissolving paracetamol in propan-2-ol at a higher temperature of 50 °C and at a stirring speed of 400 rpm. After complete dissolution of the paracetamol solute, the solid-free solution was brought to its saturation temperature \( T_S: 30 \) °C which was then recrystallized at a constant cooling rate of 0.1 °C/min at 300 rpm. At the end of the crystallization run, the resulting paracetamol crystals were kept at room temperature until the crystals were 7 to 9 mm in size. A few crystals were further grown in the growth only zone of a prepared solution \( S_0 = 1.02 \) at \( T_S: 30 \) °C. The crystals were suspended in a 70 ml solution using a crystal holder and stirred at 300 rpm at a cooling rate of 0.1 °C/min which provided approximately 80 min window for the growth only zone (GNZ). The process of crystal growth within the GNZ was repeated until sufficient growth of the seed crystals was realized. The other seed crystals are shown in Figure 5.3. These were also used in the crystallization experiments for comparison which revealed similar results. Therefore, for the experiments performed in chapter 6 and 7, only one seed crystal (Figure 5.2) was mainly used for the crystallization experiments.

Figure 5.2. SEM image of paracetamol seed crystal, size: 17.1 mm x 13.2 mm.
A crystal holder was designed using 316L stainless-steel, a material which is used in pharmaceutical and chemical processing applications due to its resistance to chemical reactions. Initially, it was experimentally tested to ensure it would not provide enhanced sites for heterogeneous nucleation during a crystallization run. To serve the purpose, a saturated solution ($S_0 = 1.0$), was split equally into two vessels with one containing a crystal holder (unseeded solution) and crystallization was simultaneously performed under the same conditions, i.e. at a cooling rate of 0.1 °C/min and 70 ml solution volume. The examinations were carried out at $T_S$: 30 and 60 °C at 300 and 370 rpm and were repeated three times. The nucleation temperature ($T_N$), i.e. the temperature at which the nucleation was first detected in a cooling process was observed in both the vessels appreciably at the same temperature with a negligible margin of ± 0.2 °C.

Figure 5.3. SEM images of different paracetamol seed crystals.
5.2. **Cooling Crystallization**

5.2.1. **Evidence of Crystal Nuclei Breeding**

The experimental evidence of crystal nuclei breeding was investigated in a cooling crystallization of paracetamol solution at a laboratory scale. A 150 ml saturated solution \((S_o = 1.0)\) was split equally into two small borosilicate vessels, with one containing a seed crystal, as shown in Figure 5.4.

![Figure 5.4. Experimental evidence of crystal nuclei breeding as a mechanism of secondary nucleation in a laboratory scale solution crystallization. Unseeded solution (left vessel), Seeded solution using a crystal holder (right vessel).](image-url)

Both the vessels were completely submerged in a transparent polycarbonate bath filled with water to enable visualization. The experimental methodology of cooling crystallization including equipment and setup is discussed in detail in chapter 6, section 6.1.1, which discusses the main crystallization experiments for the measurement of MSZW and SNT. As the solutions cooled from saturation temperature of 30 °C, secondary nucleation was detected at 21.5 °C, in a solution employed with a seed crystal. The solution in the other vessel was crystallized under influence of primary nucleation at a nucleation temperature \((T_N)\) of 10 °C. The investigation was repeated at 370 rpm and similar observations were noted in the solution with a seeded crystal, except, at \(T_N: 24.8 \) °C. Since no attrition and breakage of the seed crystal was involved during agitation, the evolution of milky white cloud in the presence of a seed crystal provided a clear evidence of nuclei breeding as the origin of secondary nucleation.
The evidence for nuclei breeding was further scrutinized through scanning electron microscopy (SEM) of the crystal seed. At the end of the crystallization run, the seed crystal was inspected, and it was observed that the surface of the seed crystal was completely covered with a white layer of particles. This possibly happened when stirring stopped, and the suspended particles accumulated on the surface of the seed crystal during settling. The seed crystal surface was then washed with a gentle stream of cyclohexane, until the surface was free from the particles. The solubility of paracetamol in cyclohexane is negligible and, it was therefore suitable to use for without the risk of any dissolution of paracetamol (De Souza et al. 2016). The investigation remarkably discovered the presence of very fine particles attached to the surface of the seed crystal, which were not visible with the naked eye. If the particles were only collected during the settlement; cleaning with cyclohexane would have been sufficient. The observations under SEM confirmed the presence of crystallites bonded to the surface of the seed crystal, as evident in Figure 5.5. This was the indication of crystal nuclei breeding, where the pre-ordered clusters from the solution attached to the surface of the seed to nucleate and then sheared off by fluid flow. The formation of a milky cloud due to particles evolution in the seeded solution and the observations made under SEM investigation provided adequate evidence to rationalize the mechanism of secondary nucleation due to crystal nuclei breeding.

Figure 5.5. Evidence of crystal nuclei breeding examined under SEM.
5.2.2. Crystal Growth

The experimental investigation of crystal growth was performed using a fresh seed of paracetamol crystal (13.7 mm x 9.14 mm) by exposing it in the growth only zone of an established MSZW of a saturated solution ($S_o = 1.0$) which was established in the present work. The surface topology of a seed was investigated, which exhibited a very smooth texture of the surface as shown in Figure 5.6. The crystal was then suspended in the vessel using a crystal holder and stirred at 300 rpm at a cooling rate of 0.1 °C/min and $T_s$: 30 °C. This provided approximately 85 min window for the growth.

![Figure 5.6. Evidence of crystal growth examined under SEM. Crystal surface topology of a fresh seed before growth (Left image), Crystal surface topology after growth, (Right image).](image)

After treating the crystal in the growth only zone, the crystal was inspected, and following observations were made. First, the growth of the crystal was apparent which was increased to 14.3 mm x 9.75 mm. Second, the growth was almost uniform in each dimension. Third, the seed was grown with a formation of a layer pattern on the surface. However, this layer pattern was observed to disappear as the crystallization progressed and crystals evolved. Similar discoveries were reported on crystal growth in which pre-critical nuclei were observed to form on the curved surface.
of a seed crystal, which on further growth became strained and then detached (Cacciuto et al. 2004). The experiment performed uncovered an interesting aspect on crystal growth, which is not just hypothesized in the growth only zone of the MSZW of a solution crystallization but evident from the SEM images of the seed crystal investigated.

5.3. Conclusion

The experiments provided evidence to rationalize crystal nuclei breeding as the origin of secondary nucleation where the pre-clusters in the solution nucleated at the surface of the seed crystal. This was evident under scanning electron microscopy with the existence of very fine crystallite layers attached to it. A uniform growth of the seed crystal was also observed within the growth only zone with the formation of a layered pattern of surface growth.
5.4. References


6. Impact of Fluid Shear Stress on Secondary Nucleation

In this work, cooling crystallization experiments were carried out at a laboratory scale using a large single seed crystal of paracetamol in a propan-2-ol solution, which was held stationary in magnetically stirred vessel with the aid of a 316L crystal holder (Figure 4.5). The experiments were performed at 300 and 370 rpm over a range of saturation temperatures for the measurements of the metastable zone width (MSZW) and secondary nucleation threshold (SNT). 300 rpm was chosen arbitrarily as a baseline agitation rate. At 400 rpm and above, the magnetic stirrer was unstable during the stirring which might have damaged the seed crystal by hitting the crystal holder. Therefore, 370 rpm was selected as the upper limit. Particle imaging velocimetry (PIV) was used to quantify the fluid turbulent shear stress (TSS) at each agitation rate employed, which was found to be 0.07 and 0.11 N/m² respectively. The TSS was determined by measuring the fluid local velocity vectors in the region of crystal suspended during the agitating process. A decrease in MSZW and growth only zone (GNZ) was observed with increasing shear stress, and the secondary nucleation threshold (SNT) was determined with a relative supersaturation ratio ($S_r$) of 1.17 at 0.07 N/m² and 1.08 at 0.11 N/m². Focused beam reflectance measurement (FBRM) displayed an increase in particle counts as nucleation progressed, with total counts increased by 25% at a higher fluid shear as more nuclei being sheared off from the seed surface under the mechanism of crystal nuclei breeding. Secondary nucleation and its link with fluid shear stress, based on a local hydrodynamics in mixing, offers a potential for a better approach in the process development.
6.1. Experimentation

Experiments were carried out at a laboratory scale for the measurement of the MSZW and SNT which was linked with turbulent fluid shear stress in a solution crystallization of paracetamol. The seed crystal used in the present investigation is the one which was used for the investigation of crystal nuclei breeding, as discussed in the previous chapter (Figure 5.2).

The solute which was used in the preparation of solution was a commercially available; monoclinic form of paracetamol (acetaminophen, 99.9% pure), which was also used for the preparation of the seed crystal. The solvents used were propan-2-ol (HPLC grade, ≥99.9% pure), also called propanol, and cyclohexane (HPLC grade, ≥99.9% pure). All the materials (solute and solvents) were obtained from Sigma Aldrich without undergoing any further purification. Cyclohexane was used as a dispersant for the measurement of particle size distribution at the end of each crystallization run. The solubility of paracetamol in cyclohexane is negligible and, it was therefore suitable to use for estimating the crystal size distribution without the risk of any dissolution of paracetamol (De Souza et al. 2016). Solubility plays an important role to interpret the mechanism of a given crystallization system and accurate data is, therefore, essential in precise measurements of the MSZW, which was taken from well-established literature. (Granberg & Rasmuson 1999, De Souza et al. 2017).


This section outlines the details of the crystallization experiments performed for the measurement of the MSZW and SNT. The experiments were carried out in a 70 ml saturated solution (paracetamol in propan-2-ol) at a low level of initial supersaturation ratio ($S_0 = 1.0$), measured in g of solute/kg of solvent, and over the range of saturation temperatures, i.e., 30 to 60 °C. At each saturation temperature, the solution was crystallized at 300 and 370 rpm under a constant cooling rate of 0.1 °C/min. To avoid concentration fluctuations in the small volumes at a given saturation temperature, initially, a large volume of solution was prepared which was then evenly used in each crystallization run. For each saturation temperature, at least twenty crystallization runs were performed, i.e. ten runs per stirring rate. After the measurement of the MSZW
(point of primary nucleation), the secondary nucleation threshold (onset of secondary nucleation) with in the MSZW was determined by repeating the same procedure. However, the solution (fresh solution) was seeded with a large crystal of paracetamol. As the solution cooled from its saturation temperature, the crystal was suspended with the aid of 316L crystal holder. All the crystallization runs were carried out under the same conditions, i.e. at a cooling rate of 0.1 °C/min and 70 ml solution volume. At both the stirring rates employed, a fluid shear stress was determined using particle imaging velocimetry which is discussed separately in section 6.1.3.

A schematic overview of the crystallization setup is shown in Figure 6.1. A 100 ml borosilicate vessel containing 70 ml saturated solution was completely submerged in a transparent polycarbonate bath filled with deionized water to enable visualization. A TX150 thermostat was programmed using LabWise 2.1.2 software to control the temperature of the water bath in combination with an immersion cooler. The set temperature was constantly monitored using a digital thermometer which was positioned near the crystallization vessel to estimate the temperature in the crystallizer. This way, the difference between set temperature and actual temperature was found within ± 0.1 °C. A MIXdrive 15 magnetic stirring plate was used for stirring in combination with a Teflon coated magnetic stirrer. The stirring rate was controlled

![Figure 6.1. Experimental illustration. (1) Laser power supply, (2) MRL-III-635L-30Mw laser, (3) Polycarbonate water bath, (4) TX150 thermostat, (5) G400 FBRM probe, (6) Immersion cooler, (7) 100 ml vessel with a seeded crystal in 70 ml propan-2-ol solution, (8) MIXdrive 15, (9) Laser detector, (10) Computer](image-url)
using a MIXcontrol 20. The onset of nucleation was detected using an MRL-III-635L-30Mw red diode laser which was calibrated to detect particles as small as 20 nm. A G400 FBRM probe was used for the real-time tracking of the particle chord length distribution and particle total counts. The measurement of the MSZW can be influenced by the type of measurement technique, (Bogacz & Wójcik 2014, Kim & Mersmann 2001, Sangwal 2011, Simon et al. 2010) and in the present work, the MRL-III-635L-30Mw laser was found to be more reliable for the experiments performed. This was experimentally tested and discussed in section 6.1.2.

The width of the metastable zone was determined by measuring the difference between the saturation temperature ($T_S$) and the temperature at which the unseeded primary nucleation was first detected by the laser, whereas, the width of the growth only zone (secondary nucleation threshold) was determined by measuring the temperature at which the secondary nucleation was first detected due to the presence of a parent crystal of the solute. Precautions were taken before the start of each crystallization run by applying a pre-treatment procedure to the seed crystal. This was done to free the surface of the seed crystal from any dust, crystallites or foreign particles which could otherwise affect nucleation. A gentle stream of cyclohexane was subjected to the seed crystal to clean the crystal surface. Secondly, at the end of a crystallization run, the SEM images of the seed crystal revealed the presence of very fine crystallites attached to its surface. Before the seed crystal would be used in the next run it was necessary to detach all the particles from the seed crystal surface as otherwise such particles would alter the MSZW measurements in the next crystallization run by serving as additional seeds. The particles were removed from the seed crystal by suspending the seed crystal in cyclohexane using a 316L stainless steel holder. The solution was stirred for at least 20 min at 400 rpm to ensure the complete removal of particles from the seed crystal surface which was further confirmed under SEM. After the crystal was treated with cyclohexane, it was dried in an oven at 50 °C for at least 30 min to ensure complete vaporization of cyclohexane or any moisture absorbed by the crystal.
6.1.2. Nucleation Detection and Laser Calibration

The detection for the onset of primary nucleation (PN) and secondary nucleation (SN), was performed with an MRL-III-635L-30Mw laser, a series of red diode lasers, which illuminates a focused beam of red light passing through the solution. The wavelength of the laser is 635 nm with an output power of 30 mW. A laser detector measured the intensity of laser power once focused on its lens. During a crystallization run, as the solution cooled from its saturation temperature, the time was referenced as zero sec and laser power was logged with respect to time. At the same time, FBRM data was logged for the tracking of particle counts. The variation of laser power and particle counts with respect to time, as shown in Figure 6.2, is presented from a crystallization run performed at 370 rpm and T\textsubscript{s}: 30 °C, for the detection of secondary nucleation. The presence of particles was detected by the decrease in the transmission of light through the solution, measured by the laser detector, which occurred approximately 52 min into cooling and at a temperature of 24.8 °C. Surprisingly, no change in the particle counts was perceived by the FBRM probe at this time. FBRM statistics for individual counts are also presented which clearly show that neither the total counts, nor the minimum detectable size from the FBRM display any change at that point.

![Figure 6.2. Experimental comparison of MRL-III-635L-30Mw laser and G400 FBRM for the detection of secondary nucleation at 370 rpm](image-url)
However, an exponential rise in the particle counts was observed after approximately 13 min, which is a temperature difference of 1.3 °C. The measurement from the two techniques can be clearly distinguished as illustrated in Figure 6.2. The power continues to decrease as the solution becomes more concentrated with particles, until the laser beam is completely blocked by the crystallized solution.

MSZW can be measured with a variety of methods such as turbidimetry, IR spectroscopy, FBRM, in-situ video probes, etc., where a turbidity-based method is widely used approach for the detection of nucleation. However, it is considered an invasive method due to in-situ monitoring. There is evidence available in the literature where different techniques used for the detection of nucleation exhibited better performance than FBRM, IR spectroscopy and other in-situ measurement methods. One such method is the use of bulk video imaging (BVI) which is an external method (Simon et al. 2010). The laser obscuration technique used in the present investigation provides good nucleation detection and can be considered external since contamination related problems are eliminated, making it a well-suited process for the measurement of the MSZW.

The investigation revealed the reliability of the laser method for the experiments performed, however, the minimum size of the particle that could be detected by the laser was currently not known. Therefore, an experiment was performed to estimate the minimum size of the particle which still could be detected. The test was performed based on the laser diffraction principle, using 20 nm particles of silicon oxide. The calibration was achieved using 0.5 mg of particles in 10 ml and 100 ml scales at a stirring speed of 300 rpm in cyclohexane. Propan-2-ol was also used as a dispersant in 100 ml volume for comparison. Initially, the investigation was performed in a small volume, i.e. 10 ml, and, the laser beam was transmitted through a stirring vial at 300 rpm and data was logged with respect to time, as shown in Figure 6.3. After eight min, 0.5 mg of silicon oxide particles were added to the vial which resulted in an instant decrease in power due to laser light obscuration. The exponential decrease in the power, for the first few min, is due to the possible clustering of very fine sized particles after which the laser intensity becomes constant due to a homogeneous suspension of particles. The calibration was then carried out at 100 ml
volume using two different dispersants which displayed appreciable results. By increasing the volume ten times, no significant change in the power was observed, as evident in Figure 6.3, which demonstrated the capability of the laser for detecting the particle size as small as 20 nm. This possibly explains the delay in the detection of nucleation using FBRM, which can measure the minimum particle size of 0.5 μm, as per the manufacturer specifications. Since the size of the particles initially formed were very small and hence, not detected by FBRM until the crystals grow to a few microns. The investigation elucidates the significance of a measuring technique which can affect the measurements of the MSZW.
Figure 6.4. Experimental illustration. (1) Computer, (2) PTU, (3) PIV laser, (4) Polycarbonate transparent bath, (5) High-speed camera, (6) Vessel with a seeded crystal in 70 ml propan-2-ol solution, (7) MIXdrive 15, (8) Real image as captured by the high-speed camera.

6.1.3. Measurement of Fluid Shear Stress Using Particle Imaging Velocimetry

Mixing via agitated vessels is commonly employed in a crystallization process and its fluid dynamics can affect the quality of the product. The fluid flow in a stirring vessel is practically not entirely uniform, even if the optimum mixing characteristics are chosen. This non-homogeneity can cause fluctuations in the velocity profile with the highest concentration near the stirrer. In the agitating vessels, the fluid flow causes friction due to viscosity, which is the primary source of shear stress in the fluids. If the fluid flow is not homogenous, the shear stress distribution is not uniform across the vessel which can affect the crystallization process. Recent investigations revealed the significance of fluid shear on secondary nucleation, with an increasing number of particles caused by more nuclei being sheared off from the surface of a seed (De Souza et al. 2016, Anwar et al. 2015). These investigations provide a vital information on crystal nuclei breeding as a possible mechanism of secondary nucleation where fluid shear is the driving force.

The present work utilized a method in which the measurements were performed to determine the shear stress based on the velocity profiles generated by rotational speeds used in crystallization experiments. An experimental set-up was arranged to replicate the crystallization experiments, as performed in section 6.1.1, and particle imaging velocimetry (PIV) was used to capture the particle flow velocities to calculate the corresponding shear stresses at the surface of the suspended crystal.
The complete arrangement is illustrated in Figure 6.4. PIV measures the entire velocity vector fields by tracking the motion of particles, by taking two high-resolution images at a small time difference of \(\mu s\). These velocity profiles were captured using a laser sheet plane illuminated by a 10,000 Hz laser with 10.6 W and a wavelength of 532 nm. A VC-Phantom v1211 high-speed camera was directed at a 90° angle to the illuminated plane to capture the images at a rate of 250 Hz. Both the laser and the high-speed camera were connected to a computer via LaVision’s universal synchronizer and a timing unit, i.e. programmable timing unit (PTU), which is controlled by the Davis software package. The vessel was placed in a transparent bath and 20 \(\mu m\) PSP polyamide particles were added in the vessel to an adequate amount to capture the velocity profiles of fluid in motion. Intensity calibration was performed along with the background image and was later subtracted from each image recorded during the test run. The essential principle of PIV is the measurement of the displacement of the particles over time, which was achieved through the cross-correlation method. This has been discussed in chapter 7, section 7.1.1.

The shear stress examined in this work is a turbulent shear stress (TSS), also called Reynolds stress (Chapter 3, equation 3.7). TSS is a time-averaged product of fluctuating velocities which was locally measured at the surface of the suspended crystal. By increasing the agitating rate from 300 to 370 rpm, the calculated shear stress was increased from 0.07 to 0.11 N/m\(^2\).

6.1.4. Measurement of Particles Count and Size Distribution

A G400 FBRM was used for in-situ measurements for tracking the particles count. The FBRM works on backscattered light signal analysis to detect chord length distribution (CLD). The characteristics of particles change over the course of nucleation. Monitoring particle chord length and count in real time provide a vital understanding of particle evolution which could be helpful in the optimization and scale-up of processes. The measurement range of the FBRM is 0.5 to 2000 \(\mu m\) as per the manufacturer specifications.

The particle size distribution (PSD) was measured using a Malvern Mastersizer 3000 analyzer at the end of each crystallization run. The filtered sample of paracetamol crystals was suspended in a cyclohexane solvent in the HydroMV of the instrument.
appropriately filled with cyclohexane, which was used as a dispersant. The laser alignment was adjusted, and a stable background signal was recorded before the addition of the paracetamol sample. The HydroMV is a separate piece of equipment which is used for the circulation of the wet suspension through the measurement window of Mastersizer. The obscuration range was ensured in the range of 7–8% to avoid any backscattering due to excess sampling. No ultrasound was used, instead, the mechanical agitation of 2700 rpm was used, which was sufficient to de-agglomerate any particles. The measurement of the particle sizes in Mastersizer ranges from 0.01 to 3500 μm as per the manufacturer specifications. In this chapter and chapter 7, all the results are presented in terms of particle mean size which reflects a mode value of a PSD.
6.2. Results and Discussion

6.2.1. Impact of Fluid Shear Stress on MSZW and SNT

The MSZW of a crystallization system can be demonstrated by isothermal and polythermal methods (Bogacz & Wójcik 2014, Kim & Mersmann 2001, Sangwal 2011). In an isothermal method, supersaturation of the solution is attained as quickly as possible, followed by the measurement of the time at which the first crystals are detected in solution. In a polythermal method, the solution is slowly cooled at a constant cooling rate until the temperature is recorded when the first crystal is detected. The results obtained from the measurements of the MSZW, using a polythermal method, are shown in Figure 6.5. These results show that the temperature of secondary nucleation was deterministic compared to the more stochastic primary nucleation.

![Figure 6.5](image.png)

*Figure 6.5. Impact of fluid shear stress on the metastable zone width (MSZW) and growth only zone (GNZ) using a large single seed of paracetamol crystal in a 70 ml saturated solution of propan-2-ol, determined using a polythermal method at a laboratory scale.*
In the crystallization process of a given system, different mechanisms of nucleation have different metastable zone limits, where the secondary nucleation has the smallest limit, followed by primary heterogeneous and largest for primary homogeneous (Lewis et al. 2015, Ulrich & Strege 2002, Kubota 2008, Kadam et al. 2012). In this work, a similar perception was unveiled from the results of the MSZW, which can be explained based on molecular kinetics. Supersaturation is the crystallization driving force which is consumed over time in a cooling crystallization of a solution. Nucleation occurs due to the clustering of solute molecules, which when reach a critical size can overcome the nucleation barrier and form a stable nucleus which subsequently could undergo further growth. The metastable zone limit at which primary nucleation occurs is the maximum supersaturation under which the solution can remain without any phase transition, which defines the wider region of a metastable zone. In secondary nucleation, this transition occurs much earlier due to the presence of a parent crystal of the solute. The surface of a parent crystal significantly lowers the nucleation barrier and hence secondary nucleation typically occurs under lower supersaturation ratios. The region between the solubility line and the secondary nucleation threshold is called the growth only zone in which de-supersaturation occurs through crystal growth rather than nucleation.

Under the same conditions and over the range of saturation temperatures investigated, a decrease in metastable zone limit and secondary nucleation threshold was measured because of increased fluid shear stress from 0.07 to 0.11 N/m². The decrease in secondary nucleation threshold was estimated by determining a relative supersaturation ratio \( S_r \) needed for secondary nucleation, which was decreased from 1.17 to 1.08 at a higher fluid shear stress. Similar conclusions were reported from the investigations of the MSZW with respect to change in an agitation rate (Kubota 2008). The relative supersaturation ratio has been calculated based on equation 2.4, which was mentioned in chapter 2.

From the investigation performed, secondary nucleation occurred due to nuclei breeding of the seed crystal employed, in which fluid shear stress was the driving force. The fluid shear stress is a force exerted by the fluid on the surface area of the seed crystal during agitation, which was increased by a factor of 1.57 (57%), corresponding to an increase in agitation rate from 300 to 370 rpm. As the seed crystal
was suspended in the solution, the pre-clusters from the solution attached to the seed surface to form crystallites and then sheared off by the fluid shear. The increased fluid shear (from 0.07 to 0.11 N/m²), therefore, resulted in a decrease in secondary nucleation threshold by increasing the probability of removing nuclei from the seed crystal surface. This is an autocatalytic process in which the newly formed crystals can also serve as a seed in turn and repeat the process (Anwar et al. 2015).

The effective metastable zone width is a powerful criterion in the design of a crystallization process. A system with a large MSZW means a large supersaturation is required for the nucleation to occur. The process of nucleation for a given crystallization system, therefore, can be controlled. For example, primary nucleation can be prevented using seed crystals in a metastable zone of the solution to have improved control over the product quality or desired end specification by introducing secondary nucleation.
6.2.2. Impact of Fluid Shear Stress on Particle Counts and Size Distribution

In the crystallization process, the characteristics of a particle change over time, monitoring the time evolution of particle count and mass deposition rate provide a vital understanding in optimization and scale-up design. FBRM is normally used for such indirect measurements of average crystal growth through monitoring the chord length of a particle during crystals evolution. In the present work, the G400 FBRM probe was primarily used to monitor the total counts and the average growth rate of particles over the course of crystallization. From the results of the MSZW, as the solution cooled from its saturation temperature of 30 °C, secondary nucleation was detected by the laser at a nucleation temperature ($T_N$) of 21.5 °C at a shear stress of 0.07 N/m$^2$ (Figure 6.6).

![Figure 6.6. Comparison of total particle counts under the influence of increased fluid shear.](image)

As the experiment progressed, an exponential rise in particle counts was observed for the first 40 min which varied linearly for the next 15 min. Thereafter, the FBRM counts did not show any substantial change in the total counts for the rest of the duration. This happened presumably due to the consumption of all the supersaturation by the seed crystal and newly formed particles, following the onset of secondary nucleation. This retarded the evolution of new particles in the process. A similar trend in the particles evolution was observed at a higher shear stress of 0.11
N/m², except secondary nucleation was detected earlier at a nucleation temperature \( (T_N) \) of 24.8 °C. The total particle counts were observed to increase by 25% with an increase in fluid shear stress. There could be a possibility of attrition enhanced secondary nucleation in crystal population however, PSD measurement revealed most of the product particles are fines less than 2.5 μm in size. Crystal attrition is not possible with seed sizes as large as 20 μm even under harsh conditions (Anwar et al. 2015). There is another convincing evidence available based on a shadowgraphy experimentation where virtually no attrition was evident using seed crystals of paracetamol as large as 355 to 500 μm (De Souza et al. 2016).

The origin of new particles, leading to an increase in counts, therefore, could only be rationalized as arising through secondary nucleation, by means of crystal nuclei breeding, since no attrition is involved in the process. The visible increase in the particles total counts with an increase in shear stress due to higher agitation resulted in an appreciable increase in the rate of secondary nucleation due to washing away of the nucleated crystallites. As the crystals from the solution nucleate at the interface of a seed surface, they are weakly bound to the surface and readily sheared off by the fluid shear. This phenomenon elucidates the implication of fluid shear stress and its link with secondary nucleation due to crystal nuclei breeding which resulted in an appreciable rise in particle counts with an increase in fluid shear stress.

The FBRM works on backscattered light signal analysis. The suspended particles in the solution backscattered the focused beam of laser light which is then detected by the probe. For the duration of the backscatter and the velocity of the optics, the chord length distribution of the particles is calculated. The rate of agitation can affect the FBRM analysis if the particles are not uniformly suspended during the agitation process and hence the FBRM statistics will not characterize the actual count in the sample. Based on a systematic experimentation, it is proved that with an increase in agitation rate, the particle counts increased up to a critical agitation rate (Dave et al. 2018). This critical point is also called the plateau value and is dependent on the mixing parameters of a given agitation system. Therefore, in the present investigation, this critical agitation rate was investigated and found to have been achieved at 250 rpm using 1.5 mg/ml sample of paracetamol in cyclohexane. The precipitated sample was collected from the original crystallization experiment performed in 70 ml solution at
300 rpm. At the end of the crystallization run, the precipitated sample was filtered and reused in 70 ml cyclohexane for suspension. The investigation was started from the minimum possible agitation rate of 100 rpm. At each agitation rate employed, as the particle counts stabilized, the particles were further suspended (stirred) for at least 20 min. Initially, the particle counts were observed to increase as the agitation rate was increased from 100 rpm and became stable at 250 rpm. With further increase in agitation rate to 300 and 400 rpm, the particle counts did not show any change in the peak value (maximum total count) as evident from the result in Figure 6.7. The experiment provided satisfactory evidence that the increase in particle total counts has only come from increased shear stress at 370 rpm rather than the particles encountered by the FBRM per unit time at a higher agitation rate.

![Graph showing effect of agitation rate on particle total counts using paracetamol sample in cyclohexane, as perceived by G400 FBRM.](image)

**Figure 6.7.** Effect of agitation rate on particle total counts using paracetamol sample in cyclohexane, as perceived by G400 FBRM.

At the end of each crystallization run, a sufficient sample of the product crystals were analyzed through laser diffraction using Mastersizer 3000. PSD data exhibited the product crystal with a mean size (mode value) of 53.4 μm at a shear stress of 0.07 N/m² which was decreased to 46.2 μm with an increase in shear stress to 0.11 N/m². Data obtained on PSD is presented on a volume basis.
The particle size distribution at both the shear stress was compared over three sets of experiments. The comparisons revealed an increasing number of fines at a higher agitation rate which was expected due to increased fluid shear. The subsequent increase in a fluid shear facilitated an increased rate of clusters detachment from the seed surface as they nucleate, which caused a higher probability of crystal nucleation over growth. Hence, comparatively more particles were formed at a smaller size. The results obtained from the sampling of three sets of crystallization runs presented an excellent repeatability of particle size distribution, as shown in Figure 6.8. This explicates the significance of secondary nucleation by allowing the uniformity in a specific form of the crystalline product due to controlled particle size distribution.

Figure 6.8. Evolution of controlled PSD and its comparison for three sets of crystallization runs, due to increased fluid shear.
6.3. Conclusion

The effective metastable zone width is an important criterion in the design of a crystallization process which can be controlled to tailor the product quality or achieve desired end specification by controlling the nucleation behavior. The investigation elucidates that the implication of measuring technique is an important factor which can significantly affect the measurements of metastable zone widths. The laser used in the present work revealed the reliability in the measurement of MSZW which can detect particle size as small as 20 nm.

With an increase in shear stress from 0.07 to 0.11 N/m², a decrease in metastable zone width and growth only zone was observed, while secondary nucleation threshold was determined with a relative supersaturation ratio of 1.17 and 1.08 respectively. As the crystals from the solution nucleate at the interface of a seed surface, they are weakly bound to the surface and readily sheared off by the increased fluid shear, which enhanced the rate of secondary nucleation and hence, resulted in a decrease in the secondary nucleation threshold.

Focused beam reflectance measurement displayed an exponential rise in the particle counts as the nucleation progressed and an appreciable increase in particle counts (25% higher) were detected at a high fluid shear i.e. 0.11 N/m² due to increase in agitation (370 rpm). This was also evident with increasing number of fines observed from the particle size distribution (PSD). The critical agitation rate was successfully achieved at 250 rpm which clearly illustrated that the increase in particle counts is negligible beyond this point (plateau value) and the 25% increase in particle total counts has evolved due to an increase in the fluid shear stress. The subsequent increase in a fluid shear enabled an increased rate of crystallites detachment from the seed surface, which caused a higher probability of crystal nucleation over growth, hence more particles were formed at a smaller size comparatively. The experiments exhibited a good repeatability over MSZW and SNT. Particularly, the revelation of controlled particle size distribution which is an important factor in the product quality elucidates the significance of secondary nucleation and its link with fluid shear stress.
6.4. References


Chapter 7: Nuclei Breeding and its Quantitative Link with Fluid Shear Stress in Mixing

7. Nuclei Breeding and its Quantitative Link with Fluid Shear Stress in Mixing

The development of robust process scale-up involves a clear understanding of mixing hydrodynamics in crystallization. In the present work, particle imaging velocimetry (PIV) was used to determine the fluid turbulent shear stress (TSS) as a function of scale-up of cooling crystallization experiments at different agitation rates. At a given scale, with increased agitation rate from 300 to 370 rpm, the secondary nucleation threshold (SNT) and product mean particle size (mode value) were observed to decrease due to increased TSS. In nuclei breeding, the nucleated crystals at the seed surface are readily sheared off by the increased fluid shear stress. This catalytic process enhanced the rate of secondary nucleation, and hence a decrease in SNT. The SNT and mean particle size increased with scale size due to a decrease in average turbulent dissipation rate (TDS) which resulted in a decrease in TSS. Secondary nucleation due to nuclei breeding was found to have a quantitative link with TSS. This resulted in a constant SNT under the influence of the same TSS which led to a consistent particle size distribution (PSD), independent of the scale. The presented approach shows that a controlled PSD can be obtained across different crystallization scales by controlling secondary nucleation through hydrodynamics.

Crystallization kinetics and its link with mixing under the influence of agitation rate has remained a considerable interest of research in the past and probably persist one of the present challenges in process scale-up. However, in the present work,
PIV was used to quantitatively link the mixing hydrodynamics with the crystallization kinetics in scale-up processes at a laboratory scale, in which the fluid shear stress is a driving factor.

7.1. Experimentation

The experimental section is divided into two parts, i.e. particle imaging velocimetry and cooling crystallization. First, PIV was used for the measurement of the fluid turbulent shear stress (TSS) at each agitation rate employed. Subsequently, cooling crystallization experiments were performed for the determination of secondary nucleation threshold as a function of TSS. Both PIV and cooling crystallization experiments were carried out in laboratory scale borosilicate glass vessels of size 100, 500 and 1000 ml. The stirring was performed using a magnetic stirrer bar of diameter 35, 55 and 64 mm respectively. The configuration of the vessel is shown in Figure 7.1.

The experimental methodology and equipment used for the cooling crystallization experiments have been replicated from the previous chapter (Yousuf & Frawley 2018), where cooling crystallization was performed using a single seed crystal of paracetamol to determine the MSZW and secondary nucleation threshold, which were linked to the fluid shear stress.

Figure 7.1. Geometric details of the borosilicate vessel.
7.1.1. Particle Imaging Velocimetry

The essential PIV methodology can be divided into three main segments. First, a fluid of known density and viscosity is seeded with homogeneously distributed particles with a nearly equal density of the fluid and sufficiently small enough to respond to the local flow movements with minimum slip. Secondly, a thin plane of a light sheet was formed by a double-pulsed laser beam to illuminate the particle in the flow. Illumination was rapidly carried out twice with a short-time delay between them. Third, a high-speed camera captured the light intensity as scattered from the particles in the illuminated plane of flow. Combining these three steps enable the determination of the time required to displace the particles over a known distance and as such enables the quantification of the velocity of the fluid.

In the present work, the flow was seeded with 20 μm polyamide particles. To ensure spatial resolution, adequate seeding of the flow is required and a minimum of 7 to 10 particles per interrogation area is recommended when using cross-correlation (Keane & Adrian 1992), which was ensured in the current experimentation. PIV measures the entire flow field by taking two high-resolution images at a small-time difference of μs. In these experiments, particles were illuminated using a double-pulsed laser sheet which was formed using a 10,000 Hz laser with 10.6 W and a wavelength of 532 nm. A VC-Phantom v1211 high-speed camera was placed at a 90° angle to the illuminated plane of light to capture the images with a resolution of 1280 x 1024 pixels. Shown in Figure 7.2 is a real image captured by the camera with the corresponding velocity vector field generated through post-processing. Both the laser and the high-speed camera were connected to a computer via LaVision’s universal synchronizer and programmable timing unit (PTU), which was controlled using the Davis software.
Figure 7.2. (a) 1280 × 1024 pixels image as captured by a high-speed camera, (b) Velocity vector field in postprocessing.
Figure 7.3. Experimental illustration of PIV setup. (1) Computer, (2) PTU, (3) Nd:YAG double pulsed laser, (4) Polycarbonate transparent bath, (5) v1211 high-speed camera, (6) Vessel with propan-2-ol solution and 316L holder, (7) MIXdrive 15, (8) 150 x 150 x 5 mm Perspex sheet.

The schematic setup of a 2D PIV system used in the present investigation is illustrated in Figure 7.3. The whole vessel was submerged in a square tank made of Perspex glass, which was filled with clean water to minimize the distortion of the laser plane through the optical arrangement. To minimize the effect of the vessel’s curvature on the optical distortion between camera and flow, a 150 x 150 x 5 mm perspex sheet was used on the top which was designed to fit the vessel. This is the most favourable arrangement of a 2D PIV system since the biggest velocity component of the flow under visualization is parallel to the plane of a light sheet while the camera viewing direction is normal to the flow (Adrian & Westerweel 2011). At first, a PIV measurement was performed at 120 ml at 300 and 370 rpm and the fluid shear stress was determined at both agitation rates. Subsequently, the measurements were performed at 580 and 1000 ml using a similar procedure and agitation rate, i.e. 300 and 370 rpm. The resultant shear stress measured at each agitation rate is summarised in Table 7.1. As expected, the resultant shear stress decreased with the scale size due to a decrease in turbulence levels and homogeneity in the flow.
Table 7.1. Turbulent shear stress measured at 300 and 370 rpm for each scale, agitated using magnetic stirrer bars of different sizes.

<table>
<thead>
<tr>
<th>Stirring Rate (RPM)</th>
<th>120 ml</th>
<th>580 ml</th>
<th>1000 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>0.071 ± 0.002 N/m$^2$</td>
<td>0.050 ± 0.005 N/m$^2$</td>
<td>0.033 ± 0.003 N/m$^2$</td>
</tr>
<tr>
<td>370</td>
<td>0.110 ± 0.003 N/m$^2$</td>
<td>0.083 ± 0.004 N/m$^2$</td>
<td>0.062 ± 0.001 N/m$^2$</td>
</tr>
</tbody>
</table>

The key in the present investigation was to determine constant shear stress at each scale that can be linked to the secondary nucleation threshold (SNT). Therefore, the agitation rate was adjusted at higher scales until the same TSS was achieved in the region of interest. For example, at 120 ml and at 300 rpm, the average TSS was calculated to be 0.071 N/m$^2$, which was achieved at 350 rpm for 580 ml and 380 rpm for a 1000 ml scale. Table 7.2 summarises the required agitation rates to achieve constant shear stress for each crystallization setup.

Table 7.2. Stirring rate required to achieve constant fluid shear stress in each crystallizer, agitated using magnetic stirrer bars of different sizes.

<table>
<thead>
<tr>
<th>Turbulent Shear Stress (N/m$^2$)</th>
<th>120 ml</th>
<th>580 ml</th>
<th>1000 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.071</td>
<td>300 rpm</td>
<td>350 rpm</td>
<td>380 rpm</td>
</tr>
<tr>
<td>0.110</td>
<td>370 rpm</td>
<td>420 rpm</td>
<td>450 rpm</td>
</tr>
</tbody>
</table>
The essential principle of PIV is the measurement of the displacement of the particles over time, which was achieved through the cross-correlation method. The recorded images were divided into sub-areas called interrogation areas or interrogation windows and using this statistical correlation technique one local displacement vector was determined for each interrogation window. In a cross-correlation technique, the displacement of the particles is measured by finding the maximum spatial cross-correlation between two interrogation regions over a known time which then produces a velocity vector (Keane & Adrian 1992, Adrian & Westerweel 2011). This process is performed repeatedly over the entire collection of images via a 2D Fast-Fourier Transform (FFT) (Keane & Adrian 1992, Adrian & Westerweel 2011, Raffel et al. 2018). The vector field was calculated with an initial window size of 32 x 32 pixel down to 24 x 24 pixel using multi-pass decreasing size postprocessing and 50 % overlap normalized correlation for high spatial resolution. The multi-pass approach with decreasing window size is an adaptive window shifting technique that allows to use a smaller final interrogation window size. Moreover, with an adaptive PIV weighing function, the interrogation window size, and shape changed automatically and optimized according to the local seeding density and flow gradients. These options improve the spatial resolution of the vector flow field and produce less erroneous vectors.

The fluid flow can be influenced by the periodic effect of stirring bar with various sampling times because PIV is based on an instantaneous flow field measurement. The average shear stress could be helpful in estimating the overall turbulence level in the region of interest. Compared to phase-resolved measurements, the phase-averaged measurements were found to be useful for depicting the overall turbulent flow structure in the mixing tank (Rutherford et al. 1996). Therefore, in the present investigation, the image rate was set to capture an image at every 10° phase shift, i.e. 36 images per revolution. A total of 1500 images were taken for each agitation rate to get the average result. The shear stress studied in this work is turbulent shear stress (TSS), using equation 3.7, which is a time-averaged product of fluctuating velocities measured locally near the surface of the crystal. This region is marked in red in Figure 7.2 (a).
7.1.2. Cooling Crystallization

Cooling crystallization experiments were carried out to determine the secondary nucleation threshold which could be linked to the fluid shear stress as determined in the PIV measurements. Crystallization experiments at three different scales, i.e. 120, 580 and 1000 ml were performed, and the PSD of the product was analysed at the end of each crystallization run, i.e., 120 mins following nucleation. As mentioned in previous chapters, the experiments were carried out using a large single seed crystal of paracetamol in a propan-2-ol solution with the aid of 316L stainless-steel holder (Figure 4.5). All crystallization runs were carried out under the same conditions, i.e. at a cooling rate of 0.1 °C/min and at a low level of initial supersaturation ratio, $S_o = 1.0$.

A schematic overview of the crystallization setup is shown in Figure 7.4 which has been replicated from the previous work as discussed in chapter 6, section 6.1.1. However, in this work, FBRM was not used for the detection of secondary nucleation.

**Figure 7.4.** Experimental illustration. (1) Laser power supply, (2) MRL-III-635L-30Mw laser, (3) TX150 thermostat, (4) Borosilicate vessel with a seeded crystal in propan-2-ol solution, (5) MIXdrive 15, (6) Immersion cooler, (7) Polycarbonate water bath, (8) Laser detector, (9) Computer.
The crystallization experiment was initially carried out at a small scale of 120 ml solution (paracetamol in propan-2-ol) at a low level of initial supersaturation ratio of $S_0 = 1.0$, measured in g of solute/kg of solvent, over the range of saturation temperatures, 30 to 60 °C. At each saturation temperature, the solution was crystallized at 300 and 370 rpm under a constant cooling rate of 0.1 °C/min. For each saturation temperature, at least five crystallization runs per agitation rate were performed. As the solution cooled from its saturation temperature, the seed crystal was suspended with the aid of a crystal holder and the time was referenced as zero sec and laser power was logged with respect to time. The onset of secondary nucleation (SN) was detected with an MRL-III-635L-30Mw. The laser technique used in the present investigation provides a good nucleation detection and can be considered non-invasive, making it a well-suited process. The measurement of the MSZW can be influenced by the type of measurement technique (Kim & Mersmann 2001, Sangwal 2011, Simon et al. 2010).

In the present work, the MRL-III-635L-30Mw laser was found to be reliable for the experiments performed which was experimentally proven in previous chapter (Yousuf & Frawley 2018), where the same approach was used for the detection of secondary nucleation.

At the end of each crystallization run, a sufficient sample of the product crystals was analysed through laser diffraction using Mastersizer 3000. The sampling method is similar which has been discussed in the previous chapter, section 6.1.4.
7.2. Results and Discussion

7.2.1. Effect of Fluid Shear Stress on SNT.

Nucleation occurs through clustering of solute molecules, which, upon reaching a critical size overcomes the nucleation barrier and form a stable nucleus that undergoes further growth. In secondary nucleation, this transition occurs at a low supersaturation due to the presence of a parent crystal of the solute.

The results obtained from the measurements of the SNT, using a polythermal method, are discussed in this section. SNT was determined with reference to the nucleation temperature ($T_N$) at which the first crystal was detected due to secondary nucleation under cooling crystallization. In general, the secondary nucleation threshold was observed to be highly deterministic. According to the nuclei breeding mechanism, the pre-nucleation clusters from solution nucleated at the seed surface to form stable crystallites which were then removed by the action of fluid shear. The increased fluid shear stress enhanced the rate of secondary nucleation by increasing the probability of crystallites detachment from the seed surface. Consequently, this resulted in a decrease in the SNT. The increased stirring rate resulted in an increase in the turbulence dissipation rate (TDS), which subsequently resulted in an increase in TSS. The increase in the turbulent dissipation rate in mixing due to the increase in agitation rate has been proposed based on a computational fluid dynamics model (Fu et al. 2018). The mechanistic insight of nuclei breeding and its link with fluid shear stress has been proven using a laboratory scale experimentation, as discussed in chapter 6 (Yousuf & Frawley 2018). From the study, the evidence of nuclei breeding was further examined through SEM, which revealed the presence of nucleated crystallites attached to the surface of the seed.

The variation of laser power over the course of a crystallization run is presented in Figure 7.5. As shown in Figure 7.5 (a), the onset of secondary nucleation was detected by the decrease in the transmission of light through the solution, which occurred at a nucleation temperature of 22 °C at 300 rpm and 24.5 °C at 370 rpm. The decrease in the SNT occurred as the fluid shear stress increased from 0.071 to 0.11 N/m², due to an increase in agitation rate from 300 to 370 rpm. Similar relationships between the MSZW and SNT with relation to a change in agitation rate have been
Figure 7.5. Detection of secondary nucleation at 300 and 370 rpm at a saturation temperature ($T_S$) of 30 °C. (a) 120 ml, (b) 580 ml, (c) 1000 ml.
documented in the literature (Yousuf & Frawley 2018, Lewis et al. 2015, Mermann 2001, Bogacz & Wójcik 2014). For 580 and 1000 ml respectively, as the agitation increased from 300 to 370 rpm, the average TSS increased from 0.05 to 0.083 N/m² and from 0.033 to 0.062 N/m². This can be interpreted in Figure 7.5 (b) and (c). The subsequent increase in a TSS at 580 ml resulted in a decrease in the secondary nucleation threshold, which changed the nucleation temperature from 20 to 22.5 °C. Similarly, at 1000 ml, an increase in a TSS resulted in a decrease in the SNT which changed the nucleation temperature from 17 to 21 °C.

A more detailed comparison is shown in Figure 7.6. As shown in Figure 7.6 (a) and (c), the average turbulent fluid shear stress (TSS) was observed to decrease with an increase in scale from 120 to 1000 ml under the influence of the same agitation rate; and hence the SNT increased. However, under the influence of the same fluid shear stress, the resultant SNT achieved was constant. This can be interpreted from Figure 7.6 (b) and (d). Though, the rate of secondary nucleation was observed to decrease slightly at the larger scale. As discussed in section 7.1.1, the aim of the present investigation was to achieve a constant secondary nucleation threshold across different crystallization scales and its impact on the product PSD. This was successfully accomplished under the influence of same fluid shear stress which was determined using PIV experimentation. For example, a constant average TSS of 0.071 N/m² achieved at each scale resulted in a constant SNT with $T_N = 22$ °C (Figure 7.6 b). Similarly, at TSS = 0.11 N/m², a constant SNT was achieved with $T_N = 24.5$ °C (Figure 7.6 d), independent of a scale.
Figure 7.6. Detection of secondary nucleation at a saturation temperature ($T_S$) of 30 °C. Comparison between agitation rate and fluid shear stress across different scales (a) 300 rpm, (b) 0.071 N/m$^2$ (continued next page)
Figure 7.6. Detection of secondary nucleation at a saturation temperature ($T_s$) of 30 °C. Comparison between agitation rate and fluid shear stress across different scales. (c) 370 rpm, (d) 0.110 N/m
A convenient way to represent the secondary nucleation threshold is by defining the relative supersaturation ratio ($S_n$). At a given saturation temperature, it can be estimated as the ratio of solution concentration at the SNT to the concentration at the solubility point. The crystallization experiments at each scale were performed over a range of saturation temperature and the corresponding SNT was determined which is shown in Figure 7.7. As the shear stress increased from 0.071 to 0.11 N/m$^2$ at 120 ml, the relative supersaturation ratio ($S_n$) decreased from 1.16 to 1.10. This figure is further split and represented in Figure 7.7 (a) and (b) for better clarification. A similar relationship was observed for the other volumes which is summarized in Table 7.3.

The investigations performed evidently reveal the quantitative influence of the fluid shear stress impact on crystal nuclei breeding, in which the TSS plays a key role. An increase in fluid turbulent shear stress resulted in a decrease in the secondary nucleation threshold by enhancing the rate of crystallite detachment from the seed surface. However, a constant SNT was successfully achieved across different crystallization scales at a same TSS.

![Figure 7.7. Impact of fluid shear stress on the SNT in 120 ml, 580 ml and 1000 ml at 300 and 370 rpm.](image)
Chapter 7: Nuclei Breeding and its Quantitative Link with Fluid Shear Stress in Mixing

Figure 7.7 (a). Impact of fluid shear stress on the SNT in 120 ml, 580 ml and 1000 ml at 300 rpm.

Figure 7.7 (b). Impact of fluid shear stress on the SNT in 120 ml, 580 ml and 1000 ml at 370 rpm.
Table 7.3. SNT determined as a relative supersaturation ratio ($S_r$), under the influence of TSS at different scales.

<table>
<thead>
<tr>
<th>Stirring Rate (RPM)</th>
<th>Supersaturation Ratio (Turbulent Shear Stress).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>120 ml</td>
</tr>
<tr>
<td>300</td>
<td>1.16 (0.071 ± 0.002 N/m$^2$)</td>
</tr>
<tr>
<td>370</td>
<td>1.10 (0.110 ± 0.003 N/m$^2$)</td>
</tr>
</tbody>
</table>
Chapter 7: Nuclei Breeding and its Quantitative Link with Fluid Shear Stress in Mixing

7.2.2. Effect of Fluid Shear Stress on PSD.

In the crystallization process, the characteristics of a particle such as crystal size, shape and purity change under the influence of different mixing conditions which can influence the product quality and effectiveness of downstream processing. These conditions can be improved by controlling the nucleation process, which requires an understanding of the optimization of the crystallization process, particularly in scale-up. The influence of different fluid shear stresses on the final PSD is shown in Figure 7.8. At a given scale, as the rotational speed increased from 300 to 370 rpm, the mean particle size (mode value) was observed to decrease. At 120 ml, the PSD data unveiled product crystals with a mean size of 49 μm which was decreased to 43 μm with an increase in TSS from 0.071 to 0.11 N/m². A similar reduction in size was found at 580 and 1000 ml, where the mean particle sizes decreased from 55 to 48 μm and from 60 to 55 μm due to an increase in TSS from 0.05 to 0.083 N/m² and from 0.033 to 0.062 N/m² respectively. The increased TSS enhanced the rate of nuclei detachment from the seed surface. This resulted in a decrease in time for the crystallites growth at the seed surface. Therefore, more crystals with smaller mean crystal size were formed in the given time span. Moreover, a more uniform (narrower) PSD was observed with increased TSS. This can be associated with an improve supersaturation uniformity in the vessel due to an increase in the turbulence dissipation rate. In a very recent study, it was shown that the mean size of paracetamol crystals was decreased with increasing agitation rates, leading to a uniform PSD (Fu et al. 2018). It was reported as the result of increased TDS which enhanced the supersaturation uniformity in the mixing.
Figure 7.8. Impact of fluid shear stress on the product PSD under the influence of same agitation rate. (a) 120 ml, (b) 580 ml, (c) 1000 ml.
The impact of fluid shear stress at each scale is also compared and presented in Figure 7.9. As the scale size increases, the mean particle size is observed to increase under the influence of the same agitation rate due to a decrease in the average fluid shear stress. Due to increased scale (volume), it is proposed that the turbulent dissipation rate was decreased, which resulted in a decrease in the TSS. This resulted in an increase in the growth rate of the crystallites before detachment from the seed surface. Therefore, a shift of the PSD to larger particles were observed. Under the influence of constant shear stress of 0.071 N/m², as shown in Figure 7.9 (a) the PSD shifted towards the left and observed to become consistent in terms of mean particle size, i.e., 49 μm, irrespective of the scale size. A similar observation can be interpreted from Figure 7.9 (b), where constant shear stress of 0.11 N/m² resulted in a smaller but consistent mean particle size of 43 μm. However, a slightly larger size of the particles was observed to form at higher scales, at a constant TSS. This can be associated with the possible increase in the availability of local supersaturation in different regions of the vessels at larger volumes. This resulted in higher growth for a few more particles comparatively. The investigation shows that it is feasible to control the secondary nucleation as which leads to the product uniformity in terms of particle size distributions, which is a key requirement in industrial crystallization.
Figure 7.9. Effect of different fluid shear stress on the product PSD in 120 ml, 580 ml and 1000 ml.
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7.3. Conclusion

Cooling crystallization experiments were performed for the measurement of the secondary nucleation threshold and PSD, which were quantitatively linked to the turbulent fluid shear stress. A scale-up was performed from 120 to 580 and 1000 ml. PIV was used to determine the fluid shear stress at each agitation rate employed.

At a given scale, the SNT was observed to decrease with an increase in turbulent shear stress. A similar trend was observed at higher scales, where SNT was observed to decrease due to an increase in the TSS. In comparison, between the scales, the SNT was observed to increase at a given agitation rate, as the scale size increased. It was anticipated since an increase in a scale resulted in a decrease in the average turbulent dissipation rate in mixing, under the same rotation speed, and hence the resultant fluid shear stress was also decreased. However, a constant turbulent shear stress resulted in a constant secondary nucleation threshold irrespective of the scale size which was achieved using particle imaging velocimetry.

At a given scale, the PSD was observed to become more uniform with a smaller mean crystal size, as the TSS was increased. In a comparison between the scales, the PSD was observed to shift right, which led to a larger mean particle size due to a decrease in the turbulent dissipation rate with increasing volume. However, under the influence of the same shear stress, PSD became consistent in terms of mean particle size. This led to a controlled particle size distribution in the scale-up performed.

The revelation of controlled particle size distribution in the scale-up elucidates the implication of mixing hydrodynamics on secondary nucleation. The approach used in the present work offers a potential for a more precise model in the process development and scale-up since nucleation is the direct consequence of nuclei breeding in which the fluid shear stress is the quantitative factor.
7.4. References

Adrian, R.J.; Westerweel, J. Particle Image Velocimetry; Cambridge University Press: New York, USA 2011.


Chapter 8

8. A Quantitative Approach in Industrial Crystallization

The development and control of robust crystallization processes in which the crystal size distribution (CSD), purity, morphology and polymorphic outcome can be predicted require a clear understanding of nucleation kinetics (Chen et al. 2011). Mechanically agitated vessels are the most commonly used equipment in industrial crystallization which requires optimum mixing parameters to produce crystals of specific properties (Celan et al. 2018, Akrap et al. 2010). The nucleation kinetics, i.e., the MSZW (primary nucleation) and SNT (secondary nucleation) of a crystallization system are sensitive to process variables such as mixing (Akrap et al. 2010, Yousuf & Frawley 2018, Yousuf & Frawley 2019, Barrett et al. 2005). Crystallization is often carried out without a detailed optimization of the hydrodynamic conditions which makes statistics on the nucleation kinetics at laboratory scale difficult to use for a reliable process scale-up (Barrett et al. 2005). However, precise knowledge of the metastable zone (MSZ), i.e., crystal nucleation and crystal growth, in the lab can reveal useful information of the likely performance of the process at the production scale.

Batch cooling crystallization is a frequently applied technique in industrial crystallization processes which reduces the solubility of the material in solution, thus, forcing material out of solution (Barrett et al. 2005). In order to interpret the mechanism of such a crystallization process, cooling crystallization experiments were performed at a laboratory scale in mechanically agitated stirred tank reactors for the measurement of SNT in a solution crystallization of paracetamol. The SNT was
quantitatively linked to the fluid turbulent shear stress (TSS) as a function of scale-up of cooling crystallization experiments. The TSS was measured using particle imaging velocimetry (PIV) by replicating the setup from crystallization experiments. Like in the previous chapters, i.e., chapter 6 and 7, (Yousuf & Frawley 2018, Yousuf & Frawley 2019), a novel systematic approach was used in the present work where a single seed crystal of paracetamol was held stationary in an agitated solution of paracetamol in propan-2-ol.
8.1. Experimentation

The mechanism of secondary nucleation due to crystal nuclei breeding (Anwar et al. 2015) under the influence of fluid shear in mixing, as discussed in the previous chapters, has been extended to the industrial crystallizers. Initially, PIV was used for the measurement of TSS at the surface of the seed crystal over a range of agitation rates. Subsequently, cooling crystallization experiments were performed for the determination of SNT as a function of TSS. Both PIV and batch cooling crystallization experiments were performed at 1 and 5 L mechanically agitated stirred tank reactors. The goal was to determine a constant TSS in scale-up that could be linked with SNT, and eventually its impact on product PSD. For all the crystallization experiments performed, the seed crystal used is shown in Figure 8.1.

![SEM image of paracetamol seed crystal](image)

**Figure 8.1.** SEM image of paracetamol seed crystal.

Cooling crystallization experiment was initially performed at a solution volume of 1 L using METTLER-TOLEDO OptiMax™ 1001 thermostat system and the scale-up was performed at 5 L using Syrris-Orb double jacketed reactor system. Both the reactors were made of borosilicate glass with torispherical bottom, which were mechanically agitated using a four-blade, 45° pitch blade turbine. The general configuration of a crystallizer is shown in Figure 8.2. The vessel has an inner diameter
of $T$ which was filled to a solution volume of height $H$. The diameter of the pitch blade turbine (PBT) impeller is $D$ with a bottom clearance of $C = 1/3H$. The crystal was held fixed at a height $Z$ from the bottom of the vessel. In order to achieve the essential scale-up rules, the geometric similarity, i.e., $D/T$, $D/H$ and $D/Z$ ratios, was maintained between the reactors which is summarised in Table 8.1.

![Figure 8.2. Geometric details of the reactor.](image)

<table>
<thead>
<tr>
<th>Scale</th>
<th>D (mm)</th>
<th>T (mm)</th>
<th>H (mm)</th>
<th>C (mm)</th>
<th>Z (mm)</th>
<th>D/T</th>
<th>D/Z</th>
<th>D/H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 L</td>
<td>41.5</td>
<td>101</td>
<td>130</td>
<td>43.3</td>
<td>70</td>
<td>0.41</td>
<td>0.59</td>
<td>0.32</td>
</tr>
<tr>
<td>5 L</td>
<td>70</td>
<td>170</td>
<td>219</td>
<td>73</td>
<td>118</td>
<td>0.41</td>
<td>0.59</td>
<td>0.32</td>
</tr>
</tbody>
</table>
8.1.1. Particle Imaging Velocimetry

Recent developments in digital photography and advancements in image analysis techniques have enabled highly capable flow visualization systems that can be used to investigate and understand extremely turbulent flow structures in mixing processes. PIV is such a very successful non-intrusive technique for instantaneous flow field measurement. The essential methodology of PIV is flow visualization, which is achieved through seeding the flow with small particles that are illuminated in a plane of pulsed light and a high-speed camera captures the light intensity as scattered from the particles in the illuminated plane of flow (Yousuf & Frawley 2019). The whole concept is to determine the time required to displace the particles over a known distance which allows the measurement of the velocity vector field in the plane of interest.

The PIV setup used in the present investigation is illustrated in Figure 8.3. The whole reactor was submerged in a square tank made of perspex glass, which was filled with clean water to minimize the distortion of the laser sheet through the optical arrangement. The flow was seeded with 20 μm polyamide particles which were illuminated with a double-pulsed laser sheet which was created using a 10,000 Hz laser with 10.6 W and a wavelength of 532 nm. A VC-Phantom v1211 high-speed camera was placed at a 90° angle to the illuminated plane of light to capture the images with a resolution of 1280 × 1024 pixels. Both the laser and the high-speed camera were connected to a computer via a programmable timing unit (PTU), which was controlled using the Davis software. The image rate was set to capture an image at every 15° phase shift, i.e. 24 images per revolution. A total of 1500 images was taken for each agitation rate to get the average result. An image captured by the camera with the corresponding velocity vector field is shown in Figure 8.4. The essential principle of PIV is the measurement of the displacement of the particles over time, which was achieved through the cross-correlation method. This method has been discussed in chapter 7, section 7.1.1 (Yousuf & Frawley 2019). The shear stress determined in this work is a turbulent shear stress, which was calculated using time-averaged fluctuating velocities measured locally near the surface of the crystal. This relationship is defined by equation 3.7 (chapter 3) (Munson et al. 2013), where \( \overline{u'} \) and \( \overline{v'} \) are time-averaged fluctuating velocity components in the 2-D flow field revealed through PIV.
\[ \tau = \rho \overline{u'v'} \]  

(3.7)

**Figure 8.3.** Experimental illustration of PIV setup. (1) Computer, (2) PTU, (3) Nd:YAG double pulsed laser, (4) Perspex box containing 1 L reactor, (5) v1211 high-speed camera.
Figure 8.4. (a) 1280 x1024 pixels image as captured by a high-speed camera, (b) velocity vector field in post-processing.
The surface of the seed crystal, illuminated for the measurement of the shear stress, is clearly visible in Figure 8.4. Shown in Figure 8.5 are the results obtained for 1 and 5 L reactor. As mentioned earlier, the TSS was calculated at both scales over the range of agitation rates. The baseline agitation rate of 425 rpm was selected for 1 L reactor, which resulted in a TSS of 0.668 N/m². At this shear stress, the required agitation rate for 5 L reactor was approximated to be 345 rpm, as shown in figure below. The initial PIV investigation was helpful in indicating a required agitation rate upon scale-up, however, in order to ensure a constant SNT, precise constant TSS was required at both scales. From the experiments, the corresponding shear stress at 345 rpm was validated, which was found to be slightly higher than the expected shear stress. Therefore, a few more experiments were repeated for 5 L reactor over a small range around 345 rpm. Repeating this procedure ultimately resulted in a required TSS, i.e., 0.671 N/m², which occurred approximately at 335 rpm. Therefore, from the experiments, a constant TSS of approximately 0.67 N/m² was achieved at 425 and 335 rpm for 1 and 5 L reactor respectively, which is tabulated in Table 8.2.
Table 8.2. Agitation rate required to achieve constant fluid shear stress on scale-up measured using four-blade, 45° pitch blade turbines.

<table>
<thead>
<tr>
<th>Scale</th>
<th>(\tau) (N/m²)</th>
<th>Agitation (RPM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 L</td>
<td>0.668</td>
<td>425</td>
</tr>
<tr>
<td>5 L</td>
<td>0.671</td>
<td>335</td>
</tr>
</tbody>
</table>

In order to validate the results of PIV measurements obtained in the presented work (Table 8.2), it was found to be interesting to compare the data from any available resources. However, according to the author’s knowledge, there were no such data available that could be used to relate the measured TSS at the crystal location. Therefore, it was encouraged to use the current PIV setup to determine the maximum turbulent shear stress at the impeller region. This could be conveniently compared with empirical relation given by equation 3.9 (chapter 3) (Mersmann 2001). Given that, this relation is only valid for turbulent flow in the vessel, PIV experiments were performed in a fully turbulent flow using 5 L reactor. The methodology implemented was analogous, however, the setup was slightly rearranged to illuminate the plane of flow at the impeller region. Moreover, the intensity calibration was performed which is usually recommended for every new experiment, particularly if it involves the distance adjustments between the camera and laser sheet. It was convenient to achieve turbulent flow at the 5 L scale which would otherwise require much higher agitation rates if 1 L reactor was used. This was not feasible with the current experimental setup.

\[
\frac{\tau_{\text{max,turb}}}{\rho(N\pi D)^2} \approx \left(\frac{P_{\text{turb}}}{2\pi^4}\right)^{2/3} \frac{DH}{TT} \left[\frac{\epsilon}{\bar{\epsilon}}\right]^{2/3} \tag{3.9}
\]

The power number (\(P_0\)) is one of the most widely used design specifications in the mixing operation for process design and scale-up, which is also known as the volumetric power draw (Ascanio et al. 2004, Paul et al. 2004). The power drawn (P) can be calculated from the torque measurements on the shaft under the influence of
the fluid forces on the impeller. The torque is usually measured by means of torque transducers which require careful calibrations for very small torque measurements in order to obtain accurate results. In laboratory scale, these measurements can be challenging since losses occurring in the agitation system can be as high as 70% of the total power supply. Therefore, other than the power drawn to the fluid, the power consumed due to friction losses should not be considered for process design or scale-up (Ascanio et al. 2004). The power number is a dimensionless quantity which is defined by equation 8.1 (Chapple et al. 2002).

\[ P_0 = \frac{P}{\rho N^3 D^5} \]  

(8.1)

Power number can be system specific due to frictional losses. In the present work, \( P_0 \) was experimentally not investigated due to lack of equipment and resources. However, the dependence of power number on Reynolds number (Re) is a well-established work, (Paul et al. 2004, Ascanio et al. 2004, Chapple et al. 2002, Xie et al. 2011) and in the fully turbulent flow, \( P_0 \) is constant and independent of the Reynolds number for a specific D/T ratio. Therefore, it was conveniently taken from the literature (Wu et al. 2006). Based on the geometrical configuration (D/T = 0.41) of 5 L reactor, \( P_{0\text{turb}} \) for four-blade, 45\(^\circ\) pitch blade turbine was found to be 1.22. The minimum agitation rate required to achieve a turbulent flow was calculated to be 376 rpm. In this work, Re > 10000 has been considered as a turbulent flow (Mersmann 2001, Paul et al. 2004). The Re was calculated using a relation defined by equation 8.2 where \( \mu \) is the dynamic viscosity of propan-2-ol in Pa s, \( \rho \) is the density in kg/m\(^3\), \( N \) is the rotational speed of the impeller in rev s\(^{-1}\) and D is the diameter of the impeller in m. The value of dynamic viscosity and density of propan-2-ol was selected at room temperature, which were taken from the literature (Pang et al. 2007).

\[ \text{Re} = \frac{\rho ND^2}{\mu} \]  

(8.2)
The maximum TSS ($\tau_{\text{max,turb}}$) was experimentally determined at the impeller region over a range of agitation rates from 400 to 550 rpm. The experiments were performed starting with an agitation rate of 400 rpm to ensure turbulent flow in 5 L reactor. Above 550 rpm, a vortex generation was observed to form near the impeller region, therefore, this was selected as the upper limit. From PIV, the maximum TSS determined at 400 rpm is shown in Figure 8.6. It is evidently visible that the maximum TSS is in the vicinity of the impeller discharged flow. Similarly, for all the agitation rates involved, the maximum TSS was determined using PIV which was then compared with the results obtained from equation 3.9. This comparison is revealed in Figure 8.7. Considering a few approximations from equation 3.9 and minor possible experimental errors from PIV, the results are found to be in a good agreement. From the investigation, the PIV setup and the methodology adopted for the measurements is considered reliable.

Figure 8.6. PIV experiment at 400 rpm in 5 L reactor which was mechanically agitated using a four-blade, 45° PBT of diameter 70 mm (a) 1280 x 1024 pixels image as captured by a high-speed camera, (b) Distribution of maximum TSS in the vicinity of impeller determined through velocity components.
Figure 8.7. Maximum turbulent shear stress in the impeller region of a turbulent flow in 5 L reactor.
8.1.2. Batch Cooling Crystallization

Cooling crystallization was initially carried out at 1000 mL solution (paracetamol in propan-2-ol). A saturated solution was prepared at 50 °C with a low level of initial supersaturation ratio of $S_0 = 1.0$, measured in g of solute/kg of solvent. A solution was prepared in accordance with solubility data which was taken from a well-established literature (De Souza et al. 2017). The solution was crystallized at a constant cooling rate of 0.1 °C/min. The baseline (reference) agitation rate employed was 425 rpm which resulted in $Re = 8960$. This is considered as the transitional regime of fluid flow in mixing, i.e., $Re < 10000$ (Mersmann 2001, Paul et al. 2004). The experiments were repeated at least three times for reproducibility. As the solution was cooled from its saturation temperature ($T_S$), the seed crystal was suspended in the solution with the aid of 316L crystal holder (Figure 4.17). The SNT was eventually determined by measuring the temperature at which the secondary nucleation was first detected due to the presence of a parent crystal of the solute. A similar methodology was adopted for the measurement of SNT involving cooling crystallization experiments for 5 L scale, which was crystallized at 335 rpm. For all the scales involved, the crystallization was performed under the same conditions, i.e., at a constant cooling rate of 0.1 °C/min, $S_0 = 1.0$ and $T_S = 50 °C$.

The general setup of an agitating reactor in a crystallization experiment is illustrated in Figure 8.8. The onset of nucleation at both scales were detected using in-situ G400 FBRM probe, which is commonly used for the real-time tracking of the particle chord length distribution. FBRM is a suitable probe-based instrument for detecting nucleation and characterizing the MSZW and, therefore, is widely used as an important tool in crystallization process development, control and scale-up (Barrett et al. 2005). During crystallization experiments, the temperature and supersaturation were also monitored. The temperature was measured using the external temperature probe available with the system and the solution concentration (supersaturation) was scrutinized continuously using in-line FTIR spectroscopy. Since supersaturation is considered as a driving force, measuring it is another vital parameter in understanding the dynamics and optimization of a crystallization process. To get a detailed understanding into the effect of process operating parameters on products PSD, a sufficient sample of the crystallized material was analysed through laser diffraction.
using Mastersizer3000 and scanning electron microscopy (SEM) using Carryscope JEOL. At the end of each crystallization run, and for all the scales performed, PSD was measured 150 mins following the nucleation event. In this chapter, the results related to PSD are presented in terms of particle mean size which reflects the mean value, i.e., D[4,3].

**Figure 8.8.** Schematic of a crystallizer setup in cooling crystallization. (1) Borosilicate vessel, (2) Temperature probe, (3) IR probe, (4) Overhead stirrer gear, (5) FBRM probe, (6) 316L stainless-steel crystal holder, (7) Seed crystal, (8) Four-blade, 45° pitch-blade turbine impeller.
The 316L crystal holders (Figure 4.17) used in the present investigation were custom designed to fit a particular reactor setup. The holder was machined using 316L stainless steel material due to its enhanced chemical resistance properties. As discussed in section 5.1, the crystal holder for the present work was also tested to ensure it would not provide enhanced sites for heterogeneous nucleation. Therefore, under the same set of thermodynamic conditions, a saturated solution was prepared at 50 °C with a low level of initial supersaturation ratio of $S_0 = 1.0$. Then cooling crystallization experiment was performed in 1 L reactor at a constant cooling rate of 0.1 °C/min and at 425 rpm. Three different sets of experiment were performed to measure the onset of primary nucleation (MSZW) and the results obtained are presented in Figure 8.9. The result from each experiment is concluded in Table 3 in terms of nucleation temperature ($T_N$), i.e., the temperature at which the nucleation was first detected in a cooling process. The investigation revealed that the presence of external interface, i.e., FBRM, FTIR and crystal holder, does have a minor influence on the onset of primary nucleation. This conforms to the intrinsic nature of primary nucleation (homogeneous and heterogeneous) as discussed in the literature, section 2.4. Due to the stochastic nature of primary nucleation, (Bogacz & Wójcik 2014, Kadam et al. 2011, Kim & Mersmann 2001) it is obvious from the results that this difference can be considered as insignificant. Besides, it is important to note that not only the crystal holder, the presence of FTIR probe does have a slight influence on the onset of nucleation. Given that, FTIR was used in all the crystallization experiments, presence of a crystal holder would not have any additional impact on the measurements. Therefore, the crystal holder was considered feasible for all the experiments performed.
Figure 8.9. Measurement of MSZW under the influence of crystal holder and in-situ probes.

Table 8.3. Comparison of MSZW over three set of experiments.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>In-situ Probes with Crystal Holder</th>
<th>MSZW (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp 1</td>
<td>FBRM ✓ FTIR ✗ Crystal Holder ✗</td>
<td>29.5</td>
</tr>
<tr>
<td>Exp 2</td>
<td>FBRM ✓ FTIR ✓ Crystal Holder ✗</td>
<td>30.5</td>
</tr>
<tr>
<td>Exp 3</td>
<td>FBRM ✓ FTIR ✓ Crystal Holder ✓</td>
<td>30.5</td>
</tr>
</tbody>
</table>
8.2. Results and Discussion

8.2.1. Effect of Mixing on MSZW, SNT, and Supersaturation.

To understand the complete characterization of the nucleation kinetics for a given crystallization process, its MSZW should be known before determining the SNT (growth only zone) within the metastable zone (MSZ) limit. Therefore, in the present work, the MSZW, i.e., primary nucleation (PN), of a batch cooling crystallization was first determined at 1 L scale using a polythermal method. After the measurement of the MSZW, the crystallized solution was heated until all the crystals were re-dissolved and a clear solution was obtained, which was then brought to its saturation temperature. At this point, as the cooling crystallization started, the solution was seeded with a large crystal of paracetamol which was held stationary in the stirring solution for the measurement of SNT. Precautions were taken before the start of each crystallization run by applying a pre-treatment procedure to the seed crystal using cyclohexane. This has been discussed in chapter 6, section 6.1.1 (Yousuf & Frawley 2018). As the solution cooled from its saturation temperature, FBRM data was logged with respect to time for the tracking of particle counts. Simultaneously, the concentration (supersaturation) of the solution was monitored through FTIR spectroscopy. All the crystallization runs were performed at a constant cooling rate of 0.1 °C/min and at T_S = 50 °C

Figure 8.10 illustrates the variation of particle total counts and the solution supersaturation profile which is presented from a set of three crystallization experiments, which was performed at 425 rpm at 1 L scale, for the measurement of MSZW and SNT. The MSZW was determined by measuring the difference between the saturation temperature (T_S) and the temperature at which the primary nucleation (PN) was first detected by the FBRM. Whereas, the SNT was determined by measuring the temperature at which the secondary nucleation (SN) was first detected due to the presence of a seed crystal. The MSZW was detected approximately 195 min into cooling and at a nucleation temperature (T_N) of 30.5 °C. While SNT occurred approximately 124 mins into cooling at T_N = 37.6 °C. At least, three sets of experiments were performed to reproduce the data, and the results are concluded in Table 8.4. These results exhibited that the SNT was deterministic compared to the
Figure 8.10. Measurement of MSZW and SNT in a batch cooling crystallization in 1 L reactor under the influence of 425 rpm. Comparison between FBRM and FTIR statistics.

more stochastic MSZW. Moreover, within the metastable zone of a crystallization system, secondary nucleation has a smaller metastable zone limit compared to primary nucleation. Similar numerous findings have been discussed in the literature (Yousuf & Frawley 2018, Yousuf & Frawley 2019, Kubota 2008, Bogacz & Wójcik 2014, Kim & Mersmann 2001, Kadam et al. 2012).

The onset of nucleation is followed by concentration changes in the solution. The MSZW and SNT could also be determined by the temperature at which the concentration (supersaturation) starts to decrease. However, the MSZW and SNT determined by this means was found to be wider for about 2 °C on average, as obvious from the Figure 8.10. This may happen because of a delay in detecting the signal for small concentration changes as the nucleation initiates. Such an observation has been reported in the literature (Akrap et al. 2010). Moreover, supersaturation measurements are difficult in cooling crystallization experiments since IR spectra is significantly affected by the change in temperature (Barrett et al. 2005). Therefore, in the present investigation, the determination of MSZW and SNT has been referenced from FBRM
statistics which measured the onset of nucleation approximately 20 mins before the maximum supersaturation could reach its peak value.

The metastable zone limit at which primary nucleation occurred is the maximum supersaturation under which the solution remained without any nucleation, which defines the wider region of a metastable zone. From Figure 8.10, this transition occurred at $S_r = 1.61$. In secondary nucleation, this transition occurred much earlier due to the presence of a parent crystal of the solute. The presence of the paracetamol seed crystal significantly lowered the nucleation barrier and hence secondary nucleation occurred at a lower supersaturation ratio of 1.40. In other words, until this point, de-supersaturation occurred through crystal growth rather than nucleation. Therefore, this region is also defined as the growth only zone which is bounded between the solubility line and the secondary nucleation threshold of a given crystallization system (Yousuf & Frawley 2018, Yousuf & Frawley 2019, Threlfall & Coles 2016). This also explains the decrease in the particle total counts under the influence of secondary nucleation. As more supersaturation was already consumed due to the presence of the seed crystal, following nucleation, the particles evolution (crystal proliferation) under the influence of secondary nucleation was retarded compared to primary nucleation.

The results presented in terms of supersaturation ratio ($S_r$) have been calculated using equation 2.4 (chapter 2), i.e., $S = C/C_{eq}$. $C$ is the concentration of the solution measured through FTIR, and $C_{eq}$ is the concentration at solubility which was taken from the work of De Souza et al (2017).

<table>
<thead>
<tr>
<th>Statistic</th>
<th>MSZW</th>
<th>SNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleation Temperature ($T_N$)</td>
<td>$30.5 \pm 0.4$ °C</td>
<td>$37.6 \pm 0.2$ °C</td>
</tr>
<tr>
<td>Supersaturation Ratio ($S_r$)</td>
<td>$1.61 \pm 0.007$</td>
<td>$1.40 \pm 0.008$</td>
</tr>
</tbody>
</table>
8.2.2. *A Quantitative Impact of TSS on SNT and PSD in Scale-up.*

The results obtained from the measurement of the SNT in a scale-up of batch cooling crystallization process, using a polythermal method, are discussed in this section. The aim was to achieve a constant SNT upon scale-up and its impact on the product PSD. This was successfully accomplished under the influence of same TSS (0.67 N/m²) which was determined using PIV, as discussed in section 8.1.1. At both scales, SNT was determined with reference to the nucleation temperature (T_N) at which the first crystal was detected by FBRM due to secondary nucleation under cooling crystallization. Moreover, the solution supersaturation was also measured using in-line FTIR spectroscopy. In general, the SNT was observed to be highly deterministic across each scale. The mechanism of nuclei breeding and its link with fluid shear stress on a scale-up has recently been proven in a laboratory scale experimentation, i.e., chapter 7 (Yousuf & Frawley 2019). In the present investigation, under the influence of same TSS of 0.67 N/m², the resultant SNT achieved was constant, irrespective of the scale. This can be interpreted from Figure 8.11. The cooling crystallization experiments at each scale were performed under the same conditions, i.e., at T_S = 50 °C and at a constant cooling rate of 0.1 °C/min. Under the influence of constant TSS of 0.67 N/m², the agitation rates employed were 425 and 335 rpm for 1 and 5 L scale respectively.

![Figure 8.11. Impact of constant TSS (0.67 N/m²) on SNT in process scale-up.](image-url)
The results in Figure 8.11 are presented from two sets of experiments for a clear interpretation and to demonstrate the reproducibility of SNT upon scale-up. At 1 L scale, the results displayed an exponential rise in particle total counts approximately for the first 60 min. Thereafter, the FBRM statistics did not show any significant change in the total counts for the rest of the duration, due to the consumption of all the supersaturation by the seed crystal and newly formed particles, following the evolution of secondary nucleation. This can be confirmed from the solution supersaturation levels measured during cooling crystallization experiments, as presented in Figure 8.12. Apparently, the trend in increase in the particle total counts at 5 L was slightly different. The rate of secondary nucleation was observed to decrease in the same time span. This tendency was also acknowledged in a previous study (Yousuf & Frawley 2019). However, the results exhibited that the supersaturation profiles have a similar trend in all the experiments, specifically, the first part of the supersaturation curves is identical. This revealed an interesting observation signifying that an increase in supersaturation is independent of the mixing parameters and scale size. In fact, it depends on the cooling rate and the solubility (Celan et al. 2018), both of which were kept constant in this investigation. As the solution cooled, the supersaturation increased linearly at a constant rate until it reached the peak value or metastable zone limit, as evident from the results in Figure 8.12. The results revealed that the maximum supersaturation at which SNT occurred was constant under the influence of same TSS, irrespective of the scale. At this point, nucleation started and the increase in total surface area due to nucleation and crystal growth consumed more and more supersaturation until it decreases to or near the solubility point. All these results are presented in Table 8.5.
Figure 8.12. Impact of constant TSS (0.67 N/m²) on supersaturation in process scale-up.

Table 8.5. Measurement of SNT and Sr in a scale-up of batch cooling crystallization, presented over three sets of experiments, under the influence of constant TSS of 0.67 N/m².

<table>
<thead>
<tr>
<th>Statistic</th>
<th>1 L</th>
<th>5 L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleation Temperature (Tₙ)</td>
<td>37.6 ± 0.2 °C</td>
<td>37.4 ± 0.3 °C</td>
</tr>
<tr>
<td>Supersaturation Ratio (Sᵣ)</td>
<td>1.40 ± 0.008</td>
<td>1.41 ± 0.002</td>
</tr>
</tbody>
</table>

From the investigations performed and based on the results presented in Figure 8.11, however, an unwelcome observation was made. The number of particle total counts generated was observed to decrease at 5 L scale. Initially, it was assumed that the uniform suspension was not achieved in the 5 L reactor, which resulted in the fraction of particles with dominant sizes to circulate at the bottom of the vessel and remained undetected by FBRM. This could be possible since at a large scale, the availability of local supersaturation increases in spatial domains which could result in a higher growth for a given volume fraction of particles in the solution. Therefore, a separate experiment was repeated at 5 L scale under the same conditions, i.e., agitation
rate of 335 rpm, cooling rate of 0.1 °C/min and at a saturation temperature of 50 °C. Like in the previous experiments, the system was cooled over the same time span. After 150 mins into nucleation, the agitation rate was increased from 335 to 500 rpm to ensure uniform suspension which was maintained for at least 10 mins. When no change in particle counts was observed, the agitation rate was further increased to 750 rpm and sustained for 10 mins. Surprisingly, no change in the particle total counts was observed. This investigation eliminated any possible misperception associated with uniform suspension, which rather suggested that the answer lies in the nucleation kinetics of the present system. To get a better insight into the process of nucleation kinetics, particle characterisation was performed by measuring the particle size distribution of the crystallised samples at the end of each crystallization run.

FBRM statistics predict the rate of particles encountered during the agitation process. The suspended particles in the solution backscattered the focused beam of laser light which is then detected by the probe. FBRM does not account for the actual number of particles in the system, rather it is the rate of particles detection. In the present work involving nuclei breeding mechanism, the rate of crystallites formation on the seed surface and then subsequent detachment is considered constant irrespective of the scale. Given that same seed crystal has been used at each scale, the number of particles generated in a given time is nearly consistent under the action of constant shear stress (0.67 N/m²) corresponding to 425 and 335 rpm. Therefore, this led to a significant decrease in particles density in 5 L scale compared to 1 L scale containing the same number of particles. Consequently, as shown in Figure 8.11, FBRM revealed a lower number of particles due to a decrease in particles exposure to the FBRM probe in a larger volume. This perhaps explains the higher rate of de-supersaturation ratio in 1 L scale comparatively (Figure 8.12) due to a high density of particles consuming more supersaturation in the given time. The outcomes of PSD analysis (Figure 8.13) in scale-up further elucidate this phenomenon.

The results obtained from the sampling of two sets of crystallization runs showed consistency in particle size distributions, as shown in Figure 8.13. This explicates the significance of secondary nucleation by allowing the uniformity in the crystalline product due to controlled particle size distribution. The PSD statistics exhibited the product crystals mean size (D₄,₃) to be very consistent across the scales
under the influence of constant TSS. The detail on PSD statistics is summarised in Table 8.6. At 5 L scale, the PSD measured also revealed the presence of particles in the coarser region. A very similar observation was revealed in PSD measurements with an increase in the scale size under the influence of same TSS (Yousuf & Frawley 2019). This can be associated with the possible increase in the availability of supersaturation levels in spatial domain, resulting in a higher supersaturation exposure to the particles, which resulted in higher growth for a few more particles comparatively. Moreover, PSD study substantiated that the actual number of particles generated in both the scales were approximately same with consistent size distribution due to a controlled secondary nucleation (nuclei breeding of a single seed crystal) under the influence of constant TSS.

Figure 8.13. Impact of constant TSS (0.67 N/m²) on product PSD in process scale-up.
Table 8.6. Particle Size Distribution Analysis Using Laser Diffraction Measurements in Scale-up of Batch Cooling Crystallization Experiments, Performed Under the Influence of Constant TSS of 0.67 N/m² and a Cooling Rate of 0.1 °C/min.

<table>
<thead>
<tr>
<th>Experiment / Scale</th>
<th>PSD Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D_{4,3} (μm)</td>
</tr>
<tr>
<td>1 / 1 L</td>
<td>334</td>
</tr>
<tr>
<td>2 / 1 L</td>
<td>323</td>
</tr>
<tr>
<td>1 / 5 L</td>
<td>336</td>
</tr>
<tr>
<td>2 / 5 L</td>
<td>371</td>
</tr>
</tbody>
</table>

The evidence of a uniform (narrower) PSD, through presented approach, is also obvious in Figure 8.14. The SEM image of paracetamol product crystals shows that the particles are of uniform sizes with very few agglomerates. The SEM image revealed the quality of crystallization process via crystal nuclei breeding of a single large seed crystal, contrary to the more typical bulk seeded batch crystallization processes. As an example of crystal nuclei breeding process in an isothermal batch seeded (using 355 to 500 μm seeds) experiments revealed a wider distribution of particle sizes, as shown in Figure 8.15 (De Souza et al. 2016). Moreover, their SEM study from a separate experiment (Figure 8.16), using 125 to 250 μm seeds, revealed many fragments in the distribution. As mentioned earlier, seed crystals are typically suspended in an agitated system, it is difficult to completely decouple crystal nuclei breeding from attrition enhanced secondary nucleation, particularly considering that seed crystals of larger sizes could break. Therefore, the presented approach is considered better in terms of a controlled crystallization kinetics, which resulted in a more uniform and consistent PSD, irrespective of the scale.
Figure 8.14. SEM image of crystallized paracetamol via crystal nuclei breeding of a large seed crystal, exhibiting uniformity in PSD.

Figure 8.15. Final product PSDs of 200, 300, and 375 rpm crystallization experiments with comparison to the seed PSD. (De Souza et al. 2016)
The goal of the present investigation was to achieve a constant SNT in process scale-up of a batch cooling crystallization and its impact on product PSD. The results evidently revealed that it is possible to control the particle size distribution of a given crystallization system by controlling its nucleation kinetics through hydrodynamics. This was successfully accomplished in the present work by controlling the secondary nucleation kinetics via crystal nuclei breeding of paracetamol in propan-2ol, under the influence of a constant turbulent shear stress. Moreover, achieving a uniform PSD is evident in the present investigation, which is a key desire in any successful crystallizing operation. A wider distribution of particle size may contain excessive fines that can be detrimental to the end stream processing.
8.3. Conclusion

In this work, the concept of controlled secondary nucleation under the influence of a constant turbulent shear stress has been investigated in a batch cooling crystallization of paracetamol in propan-2-ol. The experiments were performed to investigate the influence of constant TSS on SNT which could lead to a consistent product particle size distribution, irrespective of the scale. PIV was used to determine these turbulent shear stresses which enabled to determine the required agitation rates in a process scale-up from 1 to 5 L reactors, which was found to be 425 and 335 rpm respectively. Both the reactors were mechanically agitated using a four-blade, 45° pitch blade turbine.

The experiments were initially performed at 1 L scale to characterize the nucleation kinetics of the paracetamol solution crystallization system by measuring the MSZW and SNT. The results revealed that the MSZW occurred at a higher level of supersaturation compared to SNT. This also resulted in an increase in the number of particle total counts compared to secondary nucleation. The presence of the seed crystal significantly lowered the maximum supersaturation in the solution, hence secondary nucleation occurred with a smaller metastable zone limit compared to primary nucleation.

The investigations performed under the influence of a constant shear stress resulted in a constant SNT, irrespective of the scale. This led to a controlled particle size distribution in the scale-up performed. Moreover, a uniform PSD was revealed using nuclei breeding approach which was evident through SEM investigation. The SNT was found to have a quantitative impact under the influence of same TSS, which was determined using PIV. The results revealed that the maximum supersaturation at which SNT occurred was also constant under the influence of same TSS, irrespective of the scale. The investigations explicated that it is feasible to control particle size distribution by controlling the secondary nucleation kinetics of a given crystallization system. The novel approach established in the present work enabled a precise control over a given crystallization system. Hence, providing a potential for a better approach in process development and scale-up.
8.4. References


The work presented in this research proposes a new approach in the industrial crystallization process development and scale-up, which was quantitatively linked with the mixing hydrodynamics. The work involved systematic experiments to better understand and control the cooling crystallization kinetics, which were investigated in the solution crystallization of paracetamol. All the crystallization experiments were mainly performed for the measurement of the secondary nucleation threshold as the function of fluid turbulent shear stress using a single seed crystal of paracetamol which was held stationary in the agitating solution. The investigations performed in different cooling crystallization systems at laboratory scale revealed the quantitative impact of fluid shear stress on secondary nucleation, which resulted in a constant secondary nucleation threshold under the influence of a constant turbulent shear stress, independent of the scale. This led to a consistent particle size distribution upon scale-up which is a key requirement in industrial crystallization. The investigations revealed that it is feasible to control particle size distribution by controlling the secondary nucleation kinetics of a given crystallization system. Moreover, the presented approach proved that a uniform PSD can be obtained, which is highly desirable in a successful manufacturing process. The experiments provided clear evidence to rationalize crystal nuclei breeding as the origin of secondary nucleation where the pre-clusters in the solution nucleated at the surface of the seed crystal. These nucleated crystallites are readily sheared off by the fluid shear, which led to secondary nucleation. Therefore, SNT was found to have a quantitative impact under the influence of same TSS, which was determined using PIV. PIV is a non-intrusive measurement technique, which enabled to determine the required agitation rates in process scale-up, under the influence of same shear stress. The novel approach established in the present research offers a potential for a more precise model in the process development and scale-up since nucleation is the direct consequence of nuclei breeding in which the fluid turbulent shear stress is the driving factor. Moreover, the evolution of controlled particle size distribution in the scale-up explicates the significance of quantitative mixing hydrodynamics on secondary nucleation.
Future Recommendation

The work presented in this thesis proposes a new approach in industrial crystallization process development and scale-up. It is experimentally proved that the crystallization kinetics of a given system can be easily controlled by controlling its secondary nucleation threshold which was quantitatively linked with the mixing hydrodynamics involved. The novel approach used for the secondary nucleation via crystal nuclei breeding mechanism have revealed its significance in a successful crystallization process, which resulted in a controlled particle size distribution, irrespective of a scale. Based on the investigations performed, and some information available in the literature, some important recommendations are provided below, which will be very helpful to carry forward this approach in a more comprehensive manner.

- The work presented is system specific which involves a solution crystallization of paracetamol in propan-2-ol solvent. It is recommended that this work should be further investigated not only in other solvents using paracetamol, but also by investigating other compounds (APIs) too. This approach can be very helpful in developing robust crystallization process in different systems which will provide better understanding of the mechanism of nuclei breeding overall.

- The approach presented is entirely based on laboratory experimentation which resulted in a controlled nucleation kinetics based on quantitative measurements. However, it is encouraged to develop mathematical models to incorporate crystallization kinetics of the process involved. This can be done using a population balance model (PBM) by incorporating the rate expressions to model secondary nucleation as a surface shearing mechanism. This can provide a general mathematical model which can be a helpful indication in understanding the link between shearing (as breakage in PBM) and secondary nucleation on a fundamental level without the need of detailed experiments in the first place.
• It has been found that the power number or power input is a very important design parameter in industrial mixing and has been addressed in detail for different systems in the literature. As shown in equation 2.17 and 3.9 in this thesis, shear stress is a strong function of power number or specific power input. Therefore, it is strongly believed that for the present approach, an empirical relation for the turbulent shear stress can also be developed as a function of power number and D/T ratio. However, it is believed that a new parameter will need to be incorporated in terms of crystal bottom clearance or crystal location in the vessel. Since shear stress changes and decreases away from the impeller, it will be necessary to incorporate this factor if nucleation is based on a single fixed crystal in the crystallizer.

• As mentioned above, in order to develop an empirical relation for TSS to link with nuclei breeding mechanisms, it will require detailed experiments to measure the power input of the impeller using highly calibrated torque transducers. While doing so, it is recommended that the scale-up approach, such as power to volume ratio can be compared with the presented approach. This will be very helpful in characterizing and developing a more robust scale-up approach in industrial crystallization processes.