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Energy efficient crystallization of paracetamol using pulsed ultrasound

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ABSTRACT

This work studies the use of pulsed ultrasound during cooling crystallization of paracetamol. The effect of the pulse time on the nucleation temperature, crystal size and shape was evaluated and compared to silent conditions and continuous sonication. Most work is performed in a batch crystallizer, though some preliminary data in a recirculation configuration is also provided. In both setups, the nucleation temperature increased by at least 8 °C when ultrasound was applied compared to the non-sonicated case. When ultrasound is switched on more than 10% of the time, a similar nucleation temperature as with continuous treatment is obtained. At this minimal pulse setting, a bubble population, consisting of both oscillating and dissolving bubbles, is present in the vessel at all times. The pulse threshold can be validated using bubble dissolution calculations, and its existence leads to a vast reduction in ultrasonic energy consumption compared to continuous sonication. Finally, this work shows that the final particle size of paracetamol can be controlled in the batch setup by the pulse conditions, without affecting the crystal shape. The recirculation system shows a similar response, although further validation is recommended.

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1. Introduction

Crystallization is an important separation and purification process, often applied in chemical, petrochemical and pharmaceutical industry [1,2]. In the latter one, this process is of particular interest during the manufacturing of active pharmaceutical ingredients (APIs) [3]. The driving force for crystal formation is supersaturation of the solute which can be generated in multiple ways. Most commonly, a temperature variation or addition of an antisolvent is used [4]. Crystallization involves two consecutive steps, nucleation and crystal growth. Nucleation is the birth of microscopic crystals called nuclei, and is further classified in primary, either homogeneous or heterogeneous, and secondary nucleation. The number of nuclei formed is governed by a statistical distribution, as the process is stochastically driven. Crystal growth concerns the diffusion of molecules towards the crystal surface and the subsequent attachment on that surface. [2,5]

Industrial crystallization often prefers the use of seed crystals in order to avoid stochastic behaviour and obtain a narrow crystal size distribution [1,6]. However, for pharmaceutical applications seeding cannot always be practiced, as it is difficult to implement in sterile processes. Recently, Yang et al. showed that implementation of a temperature controlled wet mill in a continuous crystallization can also provide direct control over the particle size in steady state operation, without the use of seed crystals. The wet mill can be placed both upstream or downstream to control the amount of primary or secondary nucleation, respectively. By adequate feedback control with process analytical technology (PAT), the system can be automated to respond to perturbations or changes in the set point [7–11]. In general, a wet mill placed upstream can be used as a continuous nucleator with a short startup duration that is able to control the size and uniformity of the crystals by adjusting the tip speed. Downstream placement of the wet mill is often used to control secondary nucleation and induce crystal breakage as a means to reduce the final crystal size. The latter configuration can however increase the startup time. [11] Other ways to avoid addition of seed material is by use of T-, Y- or impinging jet mixers. These configurations produce small crystals with a narrow size distributions that can either be separated as a solid or added as a feed solution to a growth vessel when bigger crystals are desired [12–16]. A third alternative for

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seeding is the use of power ultrasound which can induce primary and secondary nucleation at low supersaturation [1,2,17–21]. All these techniques have advantages and drawbacks, depending on the API that needs to be crystallized. For example, both wet milling and ultrasound introduce heat into the solution and are therefore less suitable for temperature sensitive compounds [11,22]. Impinging jet mixers operate under high supersaturation which could lead to the production of amorphous particles. Additionally, inadequate configuration of the flowrate and angle of the two mixers could lead to clogging of the feed channels [23,24]. Despite the challenges, these techniques were successfully applied as a seeding agent to initiate the crystallization and control the final crystal size. However, it should be noted that none of these methods is impeccable and universally applicable for all APIs [24]. This work only discusses the use of ultrasound as a possible alternative for conventional seeded crystallization.

Introduction of ultrasound to a solution results in acoustic cavitation, involving the formation and implosion of micron-sized bubbles. This implosion is accompanied by several effects such as shockwaves, high temperature and pressure, microjets and improved mixing [25]. Due to these numerous effects, the main mechanism for improved nucleation by ultrasound is unknown, although several hypothesizes were proposed in literature [26]. Some authors state that the sole presence of bubbles enhances nucleation, as these act as foreign seed elements in the solution, similar to crystallization using seed crystals [27–29]. Another hypothesis claims that the high temperature and pressure, followed by rapid local cooling rates and concomitant release of shock waves, are responsible for improved nucleation under sonication [26]. Quantification of the effect of ultrasound on nucleation is performed by both induction time and metastable zone width (MZW) measurements. Lyczko et al. reported a nine fold decrease in induction time for a K_2SO_4 solution in water by application of 20 kHz ultrasound [2,30,31]. Other research showed that 45 s of sonication during cooling crystallization of lactose reduced the induction time from 10 h to 30 s [32]. Similar results were obtained by Dincer et al. who compared the induction time of lactose crystallization during sonicated and mechanically stirred experiments. Ultrasound operated at 20 kHz decreased induction time by almost ten times, depending on the supersaturation. Although agitation consumed less energy, it was not able to achieve the nucleation rates obtained using ultrasound. In addition, it was observed that a sonication time of 3 min was sufficient, as no further reduction in induction time was obtained beyond this point [33]. Similarly, ultrasound significantly decreased the induction period of the acid-base reaction crystallization of 7-amino-3-desacetoxy cephalosporanic acid (7-ACDA) [34]. Guo et al. investigated the effect of ultrasound on the metastable zone width of roxithromycin, and observed a significant reduction under sonication, attributed to an accelerated diffusion in the liquid [35]. Thompson and Doraiswamy reported an increase of at least 1.4 times in the solubility of anhydrous sodium sulphide under sonication, thus narrowing the MZW [31,36]. Although faster nucleation is often reported, the effect of ultrasound depends on the supersaturation ratio, and is most significant for low supersaturated solutions [2,35,37,38]. In addition, Miyasaka et al. concluded that a specific amount of ultrasonic energy is required to activate the improved primary nucleation [19,20]. The possibility of a threshold input was later on confirmed by similar work on the influence of ultrasonic power on the induction time of L-serine and L-arganine [38,39].

Furthermore, interesting work was published on the influence of ultrasound on crystal growth, breakage, agglomeration and polymorphism [18,40–47]. For example, Boels et al. showed that the volumetric crystallization rate of calcite could be increased by 46% under ultrasonic irradiation. The research showed that ultrasound caused attrition and fragmentation of the seed crystals, leading to a size reduction and an increase in the surface area, which in turn promoted the crystal growth rate [46]. Additionally, studies by Horie et al. and Bartos et al. showed that these fragmentation events increase at higher ultrasonic input power and longer exposure times [48,49]. Fundamental investigation of ultrasound-induced crystal breakage, i.e. sonofragmentation, identified the interaction between particles and cavitation shockwaves to be the primary mechanism for fragmentation, while other potential sources such as interparticle, particle-horn and particle-wall collisions only marginally contributed [38,47]. In the presence of surfaces that extend beyond the cavitation size, the bubbles collapse asymmetrically and create microjets in the direction of the solid [47,50,51]. This phenomenon causes pitting of the surface and generates strong shear forces that contribute to particle fragmentation. Wagterveld et al. investigated the effects of ultrasound on calcite crystals by high speed imaging and showed that jet formation can also occur in the presence of solids that are smaller than the cavitation bubbles. They hypothesized that shockwaves from bubbles collapsing nearby are able to induce the jet formation [45]. As a result, it is expected that particle breakage by ultrasound is caused by shockwaves that influence the solids through direct interaction and induced jet formation. Sonofragmentation affects the crystallization process by a reduction of the crystals present in the solution and by formation of secondary nuclei [47].

The combined effects of ultrasound during crystallization allow to 'tailor' the final crystal properties such as particle size distribution, purity, morphology and particle yield [3,17]. This approach eliminates the need for undesired post processing steps (e.g. dry milling) that can lead to safety concerns, reduced yield and additional costs. Many authors investigated this pathway by selecting appropriate operating conditions, including both conventional parameters such as the supersaturation ratio, and ultrasonic settings [1–3,18,39,52–56]. These sonication variables are usually confined by frequency and total ultrasonic intensity, the latter of which can be varied by either exposure time or power level [38,57]. Dhumal et al. reported that higher sonication intensity and longer sonication time yielded the smallest crystals below 2 mm with a narrow size distribution during an antisolvent crystallization of salbutamol sulphate particles [58]. Similarly, an increased sonication intensity during recrystallization of phenacetin reduced the particle size and resulted in an elliptical shaped crystal with an enhanced dissolution rate [53]. Kim et al. showed that a combination of in-line ultrasonic treatment at 20 kHz, and a subsequent temperature cycling protocol improved particle uniformity and modified the crystal shape of a Bristol-Myers Squibb drug substance [3]. Li et al. also stated that proper adjustment of the power density and ultrasonic treatment time provides control over the final size distribution of the crystals. They reported an inverse proportional dependency of the particle size to the sonication time and an non-linear correlation with the power density, allowing to alter the average particle size of 7-ACDA within a range of 10–30 μm [34]. Moreover, intense research on the ultrasonic crystallization of adipic acid concluded that ultrasound produces particle sizes comparable to micronization, with an even narrower size distribution [59]. In addition, it was shown that a short ultrasonic burst in the beginning of the cooling cycle yields a comparable particle size and shape as the conventional seeding process [18]. The approach of ultrasonic seeding with different exposure times and power levels was also investigated in the reactive crystallization process of cloxacillin benzathine. It was concluded that the produced needle crystals were smaller and showed less agglomeration when a longer sonication period and a higher power was used. Also, a short burst in the beginning of the crystallization, which generated in-situ seeds, was already

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