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Effect of shear rate on primary nucleation of para-amino benzoic acid in solution under different fluid dynamic conditions

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ABSTRACT

The influence of shear rate on the primary nucleation of para-amino benzoic acid in water has been investigated via a series of cooling crystallization experiments. For each experiment, we recorded the induction time at various temperatures and supersaturation ratios, employing two flow devices: a capillary tube in which the solution was divided into hundreds of monodisperse droplets and a set of stirred vials. The capillary tube was used to perform experiments in stagnant conditions (motionless droplets) and low shear rate conditions (flowing droplets), while the stirred vials were used to perform experiments at relatively high shear rates. In this way, a wide range of shear rates was investigated. Comparing the results obtained for the motionless and flowing droplets, we saw that the nucleation rate is significantly increased (by several orders of magnitude) by the shear field; however, when the shear rate increases beyond a certain level (stirred vials experiments), we observed a drop in the nucleation rate. Thus, the results demonstrate a non-monotonic dependence of primary nucleation rate on shear rate. Various mechanisms to explain the effect of shear on nucleation are quantitatively and qualitatively discussed; however, at present no definitive conclusion can be drawn to identify the controlling mechanism.

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1. Introduction

Cooling crystallization is extensively used by the pharmaceutical industry to produce and purify Active Pharmaceutical Ingredients (APIs). Crystallization consists essentially of two steps: nucleation, during which a new solid crystalline phase is formed from the liquid solution, and growth, during which solute molecules attach to the crystal nuclei increasing their size. Although the crystallization process has been known and used for decades, there is still a lack of fundamental knowledge about the nucleation mechanism, in particular under fluid dynamic conditions (Forsyth et al., 2016; Jawor-Baczynska et al., 2013). Evidence that mechanical perturbations in supersaturated solutions can trigger nucleation can be found from the beginning of the 20th century; however, systematic studies of the effect of fluid dynamics on nucleation kinetics only started in the 60s, when Mullin and Raven (1962) measured the metastable zone width (MZW) of a number of aqueous salt solutions as a function of the speed of the stirrer used to agitate them. Their results show that the MZW decreases as the agitation rate increases, reaches a minimum and then increases again. This non-monotonic behaviour was explained by the authors considering the combined effect of attrition and enhanced diffusion. More recently, Liu and Rasmuson (2013) and Liu et al. (2014, 2015) per-

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formed a series of experiments to evaluate the effect of agitation on the primary nucleation rate of *m*-hydroxybenzoic acid and butyl paraben from organic solvents using various experimental systems such as traditional stirred crystallizers, small vials agitated with a magnetic stir bar and a Couette flow system. Their results show that the induction time strongly depends on the fluid dynamic conditions in the system; however, no definitive relation between shear rate and nucleation rate was found. Forsyth et al. (2015, 2016) performed similar experiments with the aim of correlating the induction time to the mean shear rate in laminar conditions; their results suggest that the induction time can be significantly reduced by increasing the shear rate.

To explain these results, different theories have been proposed. Among these, the most popular suggested in the literature and summarised by Liu and Rasmuson (2013) are the following: shear-induced molecular alignment, enhanced mass transfer, secondary nucleation, and agitation-enhanced cluster aggregation. Liu and Rasmuson (2013) discard the first two hypotheses on the basis that solute molecules are too small to be involved in molecular alignment (Gray et al., 1995) or enhanced mass transfer phenomena. For a long time, secondary nucleation has been considered responsible for the apparent reduction of the MZW; however, while it is widely accepted that secondary nucleation reduces the time lapse between the formation of the first nucleus and the moment in which it becomes visible, it is unlikely to be the dominating mechanism. Indeed, the induction time, defined as the time lapse between the creation of supersaturation and the formation of the first stable nucleus, is usually much longer than the additional time required to detect the nucleation event. Recently, a number of studies (Jawor-Baczynska et al., 2015, 2013; Penkova et al., 2006) have supported the enhanced cluster aggregation theory, which asserts that agitation promotes the aggregation of meso-scale clusters into larger stable clusters, so that nucleation proceeds through a two-step mechanism.

Despite the number of studies, the exact mechanism controlling nucleation under fluid dynamic conditions is still unclear. One reason for the poor understanding of the problem is that, traditionally, experiments are performed in large batch crystallizers, often characterised by complex fluid dynamics and non-homogeneous temperature.

In the last decades, there has been an increasing interest in microfluidic devices, as they represent effective tools to investigate crystal nucleation kinetics in well-controlled conditions (Leng and Salmon, 2009; Rossi et al., 2015). In particular, thanks to their unique characteristics, microfluidic devices allow fundamental studies to be performed on the nucleation mechanism using the *double pulse* method, which is based on the separation of the nucleation and growth stages (Galkin and Vekilov, 1999). This is achieved by keeping the solution at high supersaturation for a certain time (*nucleation time*) and then by rapidly lowering the supersaturation ratio, thereby making the solution quickly enter the so-called metastable zone. The supersaturation level in the metastable zone is too low to allow further nucleation, but is high enough to permit the growth of the nuclei already formed. This technique has been successfully used to study the nucleation rate of APIs and organic molecules in microfluidic devices (Laval et al., 2009; Lu et al., 2015; Teychené and Biscans, 2012). One reason for the success of microfluidic devices in kinetic studies is that, thanks to their small dimensions, it is easy to achieve temperature and concentration uniformity, even without the help of a stirrer; in addition, it is possible to change the fluid temperature, and therefore the supersaturation, far more rapidly than in large-scale systems. Despite these advantages, microfluidic chips are usually very expensive, their fabrication requiring costly equipment and trained personnel. In addition, they have a fixed geometry, which cannot be modified once the chip is sealed. In contrast, transparent polymeric capillaries offer more flexibility than conventional silicon or PDMS chips.

In this work, we compare nucleation rates of para-amino benzoic acid (PABA) in water obtained in three different fluid dynamic conditions: quiescent-stagnant conditions, low-shear laminar flow and high-shear turbulent flow. To achieve these fluid dynamic conditions, we performed experiments using two fluid flow devices: a capillary tube and a set of stirred vials. Quiescent and low-shear rate experiments were performed using a transparent PTFE capillary and applying the so-called *droplet method* in conjunction with the *double pulse technique*. The *droplet method* consists in generating hundreds of small droplets of the crystallizing solution with the help of a carrier phase (in this case heptane); the *double pulse* temperature profile is then applied to the droplet array to separate the nucleation and growth stages. For the *quiescent conditions* experiments the droplets are kept motionless inside the channel, while for the *flowing conditions* low-shear experiments, the droplets are forced to move inside the channel at constant velocity, hence producing a gentle shear field. This approach has been previously used by Rossi et al. (2015), who observed that the recirculation inside the droplets slightly increased the crystal formation rate of adipic acid in water in a small range of supersaturation ratio values. The high-shear rate experiments are performed using a commercial stirred multiple reactor system (Crystal16). The above mentioned flow devices allow investigating a wide range of shear rates and can help to unveil the role of fluid dynamics in the nucleation of small molecules.

2. Methodology

Although it is well known that nucleation is a stochastic process, for large enough volumes it can be described using deterministic models. This is the case for industrial and most laboratory-scale batch crystallizers. However, this is not true when the crystallizing volume is very small (typically <1 ml), as in droplets and small vials; in this case, nucleation appears as stochastic and must be described in statistical terms.

The experimental method used in this work consists in dividing the solution into a large number of small independent volumes. In such small volumes, nucleation is a stochastic process and can be modelled using the Poisson distribution (Jiang and Ter Horst, 2011; Rossi et al., 2015), where the probability P_T that at least one stable nucleus forms in a volume V during a time t_i at a certain supersaturation level is given by:

$$P_T(t_i, V, S) = 1 - \exp\left[-JV(t_n - t_g)\right] \quad (1)$$

where P_T is the probability, J is the deterministic nucleation rate, V is the solution volume, t_i is the induction time, t_g is the growth time, t_n is the *nucleation time* and S is the supersaturation ratio, defined as the ratio between the actual and the equilibrium concentrations of the solution (c/c_e). It is worth noticing that t_i, that is, the time needed to form the first stable nucleus under the specific experimental conditions, is an intrinsic property of the system and therefore depends only on the supersaturation level and the specific system investigated, while t_g and t_n depend on the equipment used and the experimentalist. In particular, t_g is the time needed by the nuclei to reach a detectable size, while t_n represents the time lapse between the moment the desired supersaturation is achieved and the moment in which one is able to detect the first crystal. Thus, it is:

$$t_n = t_i + t_g \quad (2)$$

It is worth noting that the probability P_T tends to unity for infinite volumes. When P_T approaches unity (for a given value of t_i, this occurs when V is a few multiples of $1/Jt_i$), the nucleation process can be treated as deterministic and volume-independent.

Experimentally, we can calculate the probability distribution as the fraction of droplets that contain at least one crystal after a time t_n (for a given growth time t_g):

$$P_E(t_i, V, S) = \frac{M^+\left[t_n(t_i), V, S\right]}{M} \quad (3)$$

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