Effect of SDS on the continuous crystallization in microfluidic devices using micro-bubbles

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Introducing micro-bubbles in a microreactor for continuous crystallization increases the nucleation rate and also prevents clogging. Adding surfactants affects the micro-bubble generation as it reduces their size, increases their frequency of formation and consequently also the interfacial area per unit volume of reactor acting as heterogeneous surface for nucleation. Here, the effect of SDS on both the micro-bubble generation and the continuous crystallization of paracetamol is investigated. It is observed that while SDS significantly enlarges the heterogeneous surface available for nucleation, the crystallization itself is inhibited by its presence.

Keywords: continuous crystallization; gas-liquid interface; micro-bubbles; surfactants

1. Introduction

The presence of additives (e.g. surfactants) during a crystallization process can have substantial effects on both the nucleation and growth rates, and therefore also on the crystal habit [1]. Different effects are expected for different surfactant-crystal combinations, and due to the variety of available surfactants no suitable theoretical background to predict the effect of surfactants is available and their application is mainly based on empirical research [1, 2]. Qazi et al. studied the effect of several types of surfactant, including SDS (sodium dodecyl sulfate), on the static crystallization of sodium chloride in a micro-capillary by introducing a small volume by capillary action concluding that surfactants inhibit the crystallization by passivation of the nucleation sites [3]. In another study the nucleation rate of the single phase batch crystallization of magnesium sulfate was found to be enhanced by the addition of SDS to the liquid solution [2]. For crystal growth both enhancing as inhibiting trends are observed [1]. Another observation is that ionic surfactants tend to adsorb on preferential crystalline faces, thus influencing the growth rate in specific directions, e.g. anionic surfactants are observed to often induce needle-like crystals, which can be exploited to uniformly produce crystals in a desired shape [1, 3]. In previous research a novel way to control crystallization in microfluidic devices has been proposed [4], where micro-bubbles are continuously introduced to provide a heterogeneous surface for nucleation. And it was indeed found that introducing

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micro-bubbles in a microreactor for continuous crystallization increases the nucleation rate and also prevents clogging.

2. Experimental method

Adding surfactants to the liquid will decrease the gas-liquid interfacial tension, and therefore smaller micro-bubbles will be formed at a higher frequency, effectively increasing the interfacial area per unit volume of reactor [1]. To investigate the effect of surfactant addition (SDS (99%, J&K Scientific GmbH)), the identical experimental set-up for micro-bubble generation and crystallization as previously reported was used, see Figure 1. To quantify the effect on the micro-bubble generation, the gas (nitrogen, (99%, Air Liquide) and liquid (distilled water with different SDS wt%) were introduced via a PEEK T-junction (IDEX) connected to a horizontal glass capillary with an ID of 1 mm (OD 1.20 mm, tolerance $\pm 10\%$, CM Scientific) and 10 cm length. The nitrogen flow rate was controlled by a mass flow controller (Bronkhorst, EL-Flow®, 0.02 - 2 ml/min), and the liquid flow rate by an HPLC pump (UHP-CP Legacy, Teledyne SSI). A high-speed camera (Photron FASTCAM Mini UX100) equipped with a micro-lens (NAVITAR 1-50486) was used to record images which are then analyzed using an in-house generated Matlab script [4, 5].

For the continuous crystallization experiments a reactor of length 60 cm was used, and the HPLC pump was replaced by a centrifugal micropump (TCS Micropumps, M100S-180-V) to improve the temperature control of the supersaturated solution. The supersaturated paracetamol solution was prepared by dissolving 4 g 4-acetamidophenol (98% Acros Organics) in 200 mL ultra pure water [6]. Different SDS concentrations were investigated (0.01 wt%, 0.05 wt%, 0.10 wt%, 0.25 wt% and 0.50 wt% (critical micelle concentration (CMC) ~ 0.25 wt% [7])). The solution was heated to 80°C and stirred for at least half an hour and filtered afterwards (pore size 5-13 μm) to remove any remaining particulates (e.g. dust). A microfluidic pressure sensor (PS1-1bar, Elveflow) was used to observe the pressure drop over the reactor and two thermocouples (Omega, Type K, SC-GG-K-30-36) were installed upstream and at the outlet to know the temperature profile within the reactor. Since in this continuous crystallization experiments the reactor is not insulated the liquid temperature will decrease from its inlet to its outlet resulting in axial temperature profile and associated supersaturation degree profile along the reactor [4]. The sample is collected in a saturated solution at the reactor outlet temperature to inhibit any further nucleation. Samples are then analyzed offline using a laser diffractometer (Malvern Mastersizer 3000, small volume HYDRO SV). For details of sampling we refer to [4].

Batch experiments were performed to determine the nucleation rate subject to the SDS concentration. For this, the induction times of paracetamol-water solutions containing varying weight percentages of SDS were measured using a Crystal16 (Technobis Crystallization Systems B.V.). The Crystal16 consists of 16 reactors with a volume of 1 ml each that go through programmed cycles of heating and cooling. The Crystal16 detects changes in solution

turbidity through light transmission measurements, which indicate the formation of a crystalline phase (i.e. it only registers the formation of a large number of crystals). Before each experiment the light transmission measurement is calibrated using pure distilled water. All solutions are initially saturated at 40°C. They are heated 40°C above their saturation temperature to dissolve all ghost nuclei, and then the solutions are filtered (pore size 5-13µm) and protected from the environment to prevent impurities. In the experimental procedure, the solutions are initially cooled to 5°C to crystallize the entire solution for a first time, with subsequent heating to 80°C to again dissolve all crystals. The solution is then cooled quickly (-20°C/hr) to the desired temperature (supersaturation) and the light transmission is recorded in regular intervals to detect the onset of crystallization. The nucleation rate is then determined by calculating the experimental nucleation probability $P(t)$, defined as the ratio of the number of experiments for which nucleation has occurred before time t ($M^*(t)$) and the total number of performed measurements (M) [8]

$$P(t) = \frac{M^*(t)}{M} . \quad (1)$$

This experimental probability is then fitted to the theoretical probability that at least one crystal has been formed in time t and in a volume V [8]

$$P(t) = 1 - \exp\left(-JV(t - t_g)\right) , \quad (2)$$

where J denotes the nucleation rate, and t_g is the growth delay time that is required for crystals to grow to a detectable size.

Figure 1. Experimental setup for crystallization: (1) feed solution, (2) water for cleaning the system and (3) sample collection. Samples are analyzed offline with a laser diffractometer. The inserted images on the right show the size difference of micro-bubbles for two different cases. Reprinted with permission from Fatemi et al.[4] Copyright 2019 American Chemical Society.

3. Result and Discussion

Surfactant addition is expected to influence the hydrodynamics of the micro-bubble generation and of the bubble flow. The micro-bubble size, micro-bubble generation frequency, micro-bubble velocity and the resulting bubble surface area per unit volume of reactor were quantified by analyzing the images taken with a high-speed camera (Figure 2). As it is observed in Figure 2(a), adding SDS reduces the bubble diameter by 50%, and at the same time increases the bubble generation frequency by a factor of 5 (Figure 2(b)). The bubble breaks off when the shear forces exceed the surface tension forces, and adding SDS lowers the surface tension drastically [9, 10]. Furthermore, the addition of SDS also results in reduced bubble velocities (Figure 2(c)), resulting in a slip ratio of 1 between the two phases (Table 1), meaning that the two phases travel at the same local velocity within the micro-reactor (without surfactant the slip ratio is 1.25 [4]). The surfactant adsorbed on the interface moves from the front to the rear point of the bubble due to surface advection [11, 12]. This shear stress increases the drag resulting in the velocity to decrease compared to the system without any surfactants present. Furthermore the unequal surfactant distribution over the interface induces a surface tension gradient resulting in Marangoni effects which opposes the surface flow which rigidifies the interface and increases the drag coefficient [11, 13, 14]. This rigidified interface results in the observed no-slip condition at the interface. Finally, this surfactant related effect results in an increase in the bubble surface area per unit volume of reactor by a factor of 2, see Figure 2(d).

The effect of bubbles on the continuous crystallization of paracetamol was investigated by comparing the obtained crystal size distributions (CSD) for liquid flow rate of 1 ml/min and gas flow rate of 0.05 ml/min with and without presence of SDS for a supersaturated solution with supersaturation ratio of $S=1.81$. The supersaturation ratio is defined as the ratio of the solubility at the specified feed temperature to the solubility at room temperature. Measurements were carried out at three different times where the crystals have been growing for respectively one, four and seven minutes after sample collection. The crystals flowing out of the reactor are collected in a saturated solution, which stops nucleation but still allows for crystal growth. These times are dictated by the sample preparation for the laser diffractometer measurement. The results for the system without any SDS at different growth times is shown in Figure 3 with and without micro-bubbles. Nucleation in the presence of micro-bubbles results in larger crystal sizes also during growth compared to the system without any bubbles, but the relative difference in size becomes smaller, which indicates that the growth rate is larger compared to the nucleation rate [4]. Each set of experiments was performed at least in triplicates, and three consecutive measurements were carried out by the laser diffractometer for each sample.

Figure 2. Effect of SDS wt% on (a) size of the micro-bubbles, (b) frequency of micro-bubble generation, (c) micro-bubble velocity, (d) micro-bubble surface area per unit volume of the reactor for different liquid flow rates at room temperature and at constant gas flow rate $G=0.05$ ml/min for ($\times$) water, ($+$) water+SDS(0.01wt%), ($\triangle$) water+SDS(0.05 wt%), ($\square$) water+SDS(0.1wt%) and ($\circ$) water+SDS(0.5 wt%).

Table 1. Overview of the slip ratios for different SDS wt% for a liquid flow rate of $L=1$ ml/min and a gas flow rate of $G=0.05$ ml/min.

	water	water- SDS			
		0.01 wt%	0.05 wt%	0.1 wt%	0.5 wt%
Slip ratio	1.25	0.95	0.96	0.96	0.97

Figure 3. Effect of the growth time on the CSD for crystallization with ($G=0.05$ ml/min; $L=1$ ml/min) and without ($L=1$ ml/min) micro-bubbles at a supersaturation ratio of $S=1.81$. Reprinted with permission from Fatemi et. al.[4] Copyright 2019 American Chemical Society.

For the system with SDS, crystals were detected only after 4 minutes growth time clearly showing that the presence of SDS is inhibiting the nucleation, see Figure 4(a). Without SDS, detectable crystals were measured with the laser diffractometer after only 1 minute of growth time [4]. With increasing surfactant concentration the peak is shifting more to the left. As shown earlier, adding the micro-bubbles results in larger crystals at identical residence and growth times, which indicates that nucleation is induced earlier (reduced induction time) and that the gas-bubble interface acts as a heterogeneous nucleation site [4]. However, despite increasing the heterogeneous surface area per unit volume of the reactor (see Figure 2(d)), it seems that adding SDS is inhibiting these sites to act as a nucleation site. Furthermore, there is hardly any difference in CSD for the CMC concentrations and above since already the surface of the bubble is covered with SDS. The same trend is observed for 7 minutes growth time, see Figure 4(b).

To quantify the obtained crystal sizes, Table 2 shows the mean crystal size based on volume, $Dv(50)$, together with the $Dv(10)$ and $Dv(90)$ values, denoting that 10, respectively 90 percent of the crystals are below a certain size. Furthermore, the span of the CSD is calculated as

$$span = \frac{Dv(90) - Dv(10)}{Dv(50)}. \quad (3)$$

Figure 4. Effect of SDS on the crystal size distribution in two phase bubble flow for a supersaturation of $S=1.81$: (a) 4 min growth, (b) 7 min growth. The liquid flow rate was $L=1$ ml/min, and the gas flow rate $G=0.05$ ml/min.

Table 2. Effect of different SDS wt% on the $D_v()$ values of the crystal size distribution for a liquid flow rate $L=1$ ml/min and a gas flow rate $G=0.05$ ml/min and a growth time of 4 min.

SDS wt%	Dv(10)			span
	[μm]	Dv(50) [μm]	Dv(90) [μm]	
0	44.43±7.61	147.72±17.93	288.69±31.73	1.65
0.05	22.06±3.93	78.81±19.57	220.22±38.06	2.51
0.1	22.17±3.65	86.14±13.31	232.01±36.10	2.44
0.25	16.16±6.01	57.02±29.41	218.75±54.69	3.55
0.5	13.12±5.67	58.73±27.98	210.30±46.93	3.36

After 4 min growth time 50 % of the particles without the addition of SDS are below $147 \mu\text{m}$, which for the lowest SDS concentrations of 0.05 wt% drops to $79 \mu\text{m}$ and for the highest SDS concentration of 0.5 wt% is $58 \mu\text{m}$ almost dropping to one-third its size. While the presence of SDS decreases the mean crystal size it increases the span and broadens the CSD. Furthermore for 7 min growth time, see Figure 4(b), for higher concentrations of the surfactants the distribution shifts to the left but less pronounced compared to Figure 4(a). As mentioned earlier after 1 minute growth time detectable crystals could only be measured for the system without SDS which was not the case when SDS is present, however after giving it a certain growth time detectable crystals could be measured for both the systems with and without SDS. And with more growth time the relative difference between the two systems become smaller. The broadened CSD suggests that the inhibiting effect of SDS is mainly

relevant for nucleation in two-phase flow and not for the growth phase. The formation of nuclei occurs at different times on different bubbles, thus leading to this broadened CSD. After 7 min growth time the mean size of the particles for 0 wt% SDS are below $166\ \mu\text{m}$, which for the lowest SDS concentrations of 0.05 wt% drops to $127\ \mu\text{m}$ and for the highest SDS concentration of 0.5 wt% is $104\ \mu\text{m}$. At SDS wt% of 0.25 and 0.5 which are at and above CMC respectively, hardly any difference is observed. As mentioned earlier, with SDS concentrations above the CMC the nucleation sites are blocked for any further nucleation which results in similar CSD for different growth times.

To further investigate the reduced nucleation in the presence of SDS batch experiments were performed using the Crystal16. Figure 5 depicts the experimentally obtained cumulative nucleation probability curves as a function of the induction time for a supersaturation of $S=2.65$ and for varying SDS content of 0 wt%, 0.01 wt%, 0.05 wt%, and 0.1 wt%. As it is evident from the experiments, with increasing SDS concentration the induction time is increased and the nucleation probability is reduced. To further quantify these findings, the fitted nucleation rates at different supersaturations S and SDS content are reported in Table 3. For 0.01 wt% SDS nucleation is observed at all investigated supersaturations, however the nucleation rate is drastically reduced compared to the case without SDS. At higher SDS content no crystals are observed for a supersaturation below $S=2.12$. Thus, these batch experiments proof that SDS hinders nucleation for the single phase cooling crystallization of paracetamol.

To translate this observation to the continuous cooling crystallization a comparison was made for both single-phase and two-phase flow, see Figure 6, for a SDS concentration of 0.05 wt% and at a supersaturation ratio of 1.81. As clearly seen from Figure 6 the two-phase bubble flow without any SDS has the largest crystal sizes and the one-phase system (no micro-bubbles present) with SDS has the smallest crystal sizes. This shows that adding micro-bubbles to the system enhances the nucleation while adding SDS inhibits it in both single and two-phase flow. The continues crystallization experiments also again provided proof that the micro-bubbles increase the nucleation, however, when SDS is added, the additional increase in interfacial area due to the smaller micro-bubbles does not counteract the nucleation suppression due the presence of SDS.

Figure 5. Cumulative nucleation probability curves subject to the induction time at a supersaturation of $S=2.65$ and for varying SDS content. The experiments are performed in 1 ml batch reactors (Crystal16). The fitted theoretical curves are represented by lines.

Table 3. Nucleation rates at different supersaturations S and SDS content. The experiments are performed in 1 ml batch reactors (Crystal16).

SDS wt%	Super- saturation S	Nucleation rate $J [\text{s}^{-1} \text{m}^{-3}]$	95% confidence interval
0	1.64	86.34	79.83-92.82
	1.93	546.7	468.5-624.9
	2.65	2333	974.4-3691
0.01	1.64	62.49	45.7-79.27
	2.12	131.4	91.3-171.6
	2.65	247.1	197.6-297.7
0.05	1.64	no crystals	
	2.12	no crystals	
	2.65	89.55	66.54-112.6
0.1	1.64	no crystals	
	2.65	30.56	19.33-41.79
	3.09	770.6	412.6-1129

Figure 6. Effect of SDS on crystal size distribution in single phase and two-phase flow with presence of SDS for liquid flow rate $L=1$ ml/min and gas flow rate $G=0.05$ ml/min for a supersaturation of 1.81 for 4 min growth time.

This was further investigated by recording the pressure drop during clogging of the reactor for a highly supersaturated solution with a supersaturation ratio of 2.14, see Figure 7. The system with no SDS and no micro-bubbles was clogged after only couple of minutes of continuous experiments. Adding micro-bubbles prolongs the continuous operation time, but the longest operation time was found for the system using SDS without any bubbles. This is linked to the fact that the nucleation is inhibited when using SDS, and therefore less crystals are formed, reducing the clogging tendency. Adding micro-bubbles to the SDS system again reduces the operation time, the added interfacial area will act as nucleation increasing the number of crystals. However, this effect is still less expressed as for the case without SDS.

Figure 7. Reactor inlet pressure for the continuous crystallization with ($G=0.05$ ml/min; $L=1$ ml/min) and without ($L=1$ ml/min) micro-bubbles at a supersaturation ratio of $S=2.14$.

4. Conclusion

In summary, micro-bubbles enhance nucleation by introducing a heterogeneous site for nucleation, however, adding the SDS showed a decrease in the nucleation despite increasing the bubble surface area per unit volume of the reactor. The presence of SDS hinders nucleation and the higher the SDS concentration, the more this effect is pronounced and cannot be balanced by providing more interfacial area in the continuous crystallizer.

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Symbols used

CMC	[-]	critical micelle concentration
CSD	[-]	crystal size distribution
$Dv(x)$	[-]	x percent of the crystals are below a certain size
G	[ml/min]	gas flow rate
ID	[mm]	inside diameter
J	[$s^{-1} m^{-3}$]	nucleation rate
L	[ml/min]	liquid flow rate
OD	[mm]	outside diameter
S	[-]	supersaturation degree
SDS	[-]	sodium dodecyl sulfate

t	[s]	time
tg	[s]	growth delay time
V	[ml]	volume
wt	[%]	weight percent

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