

Determination of the effect of the ultrasonic frequency on the cooling crystallization of paracetamol



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ABSTRACT

This paper presents a study on the effect of ultrasonic frequency on both the nucleation and the degradation of paracetamol under sonication. The effect of ultrasonic irradiation was investigated for frequencies ranging from 41 to 1140 kHz. The results obtained in this paper show that the lower ultrasonic frequencies are preferable, both to enhance the nucleation rate and to limit degradation. A reduction of the metastable zone width was observed in all experiments when applying ultrasound. The highest reduction was achieved at a frequency of 41 kHz and a decrease of the reduction was observed with increasing ultrasonic frequencies. Degradation was limited at a frequency of 41 kHz, while significantly higher levels of degradation are observed at higher frequencies. Radical formation seems to be the main degradation mechanism for all frequencies.

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1. Introduction

Crystallization is a widely used technique for the production and separation of pharmaceuticals and fine chemicals [1–6]. The application of ultrasound in these crystallization processes has shown positive effects on the nucleation of both organic and inorganic components. Several papers report a reduction of the induction time at lower supersaturation levels, a reduction of the metastable zone width (MZW), the formation of smaller particles and an increase of the reproducibility of the particle size distribution after ultrasonic irradiation [3,7–11]. Most of the sonocrystallization experiments reported in literature are performed in commercially available equipment with fixed ultrasonic frequencies ranging from 20 to 100 kHz [3,12–15]. Because of this fixed parameter, the effect of it on the crystallization reaction is rarely investigated.

Only a few papers studied the impact of the ultrasonic frequency on the crystallization process. Li et al. tested the sonocrystallization of spectinomycin hydrochloride during ultrasonic irradiation at 15, 20, 25 and 30 kHz [14]. An ultrasonic horn with a titanium probe tip of 8 mm was used in a 15 mL solution. The power output was set at 400 W during all experiments. No significant differences in crystal size or shape were observed when varying these

frequencies. Therefore it was concluded that all frequencies have the same influence on the nucleation and growth of the crystals. Somewhat higher frequencies were tested by Wohlgemuth et al. [16]. The impact of ultrasound at 204, 355.5 and 610 kHz on the MZW and crystal size distribution was investigated during the crystallization of adipic acid. A power of 200 W was applied to an ultrasound transducer placed at the bottom of a 1.2 L reaction vessel. The transducer had a diameter of 100 mm. No dependence of the MZW on the frequency was observed, although smaller crystals are reported at lower frequencies. A bimodal distribution was visible in the graph of the particle size distribution. The second peak of the particle size distribution was shifted from 500 μm to 300 μm by varying the ultrasonic frequency from 610 to 355.5 kHz. This effect was explained by a reduction of agglomeration of the crystals at lower frequencies. It was assumed that the growth kinetics were changed by applying ultrasound, which resulted in changes in the crystal shape and consequently reduced agglomeration. It is, however, still unclear how ultrasound impacted the growth kinetics. Increased mass transfer due to enhanced micro-mixing under sonication is the most commonly used explanation in literature [17]. Kordylla et al. investigated the effect of the ultrasonic frequency and power on the cooling crystallization of dodecanedioic acid [18]. Two different frequencies of 355.5 and 1046 kHz were tested in the same reactor setup as Wohlgemuth et al. The authors performed calorimetric measurements and it was observed that for the same power supplied to the transducers, the power inside the reaction medium was dependent on the applied ultrasonic frequency. The calorimetric power was therefore not constant

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between the different frequencies and no conclusions could be formulated about the effect of the frequency on the MZW. Furthermore, a decrease of the MZW was reported in the same paper with increasing power inside the reaction medium. The experiments were performed at output powers of 100 and 200 W for all frequencies. These observations, together with other papers about sonochemical reactions, show the importance of keeping the power inside the solution constant when comparing different frequencies [18–21].

Each of these three papers investigated the effect of the frequency on a rather limited frequency range. It could be expected that the effect on the type and size of cavitation bubbles is rather limited in this range [22]. Furthermore, it is difficult to mutually compare the results of these papers because of the different powers, products and reactor geometries. To make a general conclusion, the effect of the frequency should be tested with constant power in one reactor geometry on one product.

Besides an enhancement in crystallization, ultrasound is also capable of creating degradation. It is known that ultrasound can degrade organic compounds such as paracetamol [20,23,24]. Ultrasonic degradation can be caused by pyrolytic degradation of the investigated compound or via $\bullet\text{OH}$ radicals formed by implosion of the cavitation bubbles. The route of degradation is dependent on the physical and chemical properties of the organic compound. Volatile aromatic components undergo mainly pyrolytic degradation, while aromatics with hydrophilic characteristics are degraded predominantly via the radical chain mechanism. Isariebel et al. investigated the degradation of paracetamol by sonication in the frequency range of 574–1134 kHz and showed that degradation takes place by the reaction with radicals [20]. This reaction takes place at the interface of the cavitation bubble and consists of two steps. First $\bullet\text{OH}$, $\text{H}\bullet$ and $\text{HOO}\bullet$ radicals are formed within the cavitation bubble by the sonolysis of H_2O and O_2 . Secondly, these radicals move to the bubble interface to react with the organic compounds or they recombine to form H_2O or H_2O_2 . The degradation rate depends on the frequency as it impacts the amount of radicals formed inside the bubbles and released into the liquid. On the one hand, the cavitation effects are more violent at low frequencies, leading to a higher production of radicals. On the other hand, most radicals will recombine inside the cavitation bubbles at these low frequencies due to the long lifetime of collapse. At higher frequencies, the energy released upon collapse is reduced and consequently the yield for formation of radicals diminishes. However, the collapse occurs more rapidly and more radicals are able to escape from the bubble before they recombine. An optimum exists typically at a frequency between 200 and 600 kHz [24,25]. During crystallization, this degradation is unwanted as the presence of impurities can create problems during the production of pharmaceutical components [5,6,26]. Significant inhibition or promotion of the crystal growth and the appearance of multiple nucleation bursts at the presence of even trace amounts of impurities are reported by Nagy et al. [5]. Consequently, these impurities can have a significant impact on the MZW and the size and shape distributions of the final products [4–6]. Therefore it is important to consider the influence of the ultrasonic frequency on the degradation of paracetamol during crystallization experiments.

The purpose of this paper is to gain more insight in the effect of the ultrasonic frequency on the nucleation of paracetamol. For the first time, the effect of ultrasound on the MZW was investigated within a broad frequency range of 41–1140 kHz in one single reactor geometry. In contrast to previously reported experiments, the power inside the reaction medium was kept constant for all frequencies. Furthermore, the sonochemical degradation of paracetamol was investigated under the same reaction conditions. Finally, the optimal ultrasonic frequency for enhancement of the nucleation was defined based on both results.

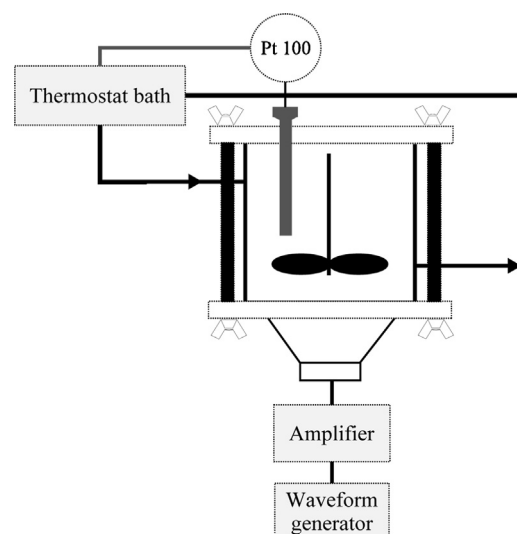


Fig. 1. Reactor setup.

2. Materials and methods

2.1. Experimental setup

Fig. 1 shows the setup which consists of a jacketed glass reactor without bottom plate, a top plate and ultrasound transducer. This transducer is placed at the bottom of the reactor and clamped to the top plate to allow proper sealing of the reactor. By clamping different transducers to the bottom, each operating at its resonance frequency, it is possible to use the same reactor over the complete frequency range.

Three different ultrasound transducers were used, one with resonance frequencies of 41 and 98 kHz (Ultrasonics World MPI-7850D-20.40.60H), another with a frequency of 165 kHz (Ultrasonics World MPI-4235D-235H) and a third with frequencies of 570, 850 and 1140 kHz (Meinhardt E/805/T/M). The first two transducers were glued to a glass plate to avoid corrosion and erosion of the transducer surface. The last one was a transducer with titanium diaphragm which could directly be used.

The ultrasonic frequency and power were controlled by a Picotest G5100A waveform generator which was connected to an E&I 1020L RF power amplifier which drives the ultrasound transducers.

The temperature was controlled by a Julabo FP45-ME thermostat bath and a Pt100 thermocouple. A Cole Parmer ultra compact mixer with axial blade impellor was used to stir the solution at 400 rpm.

2.2. Calorimetric measurements

First, the resonance frequencies of the transducers were defined by a Sine Phase impedance analyzer 16,777 K. During these measurements, the transducers were clamped to the reactor, 150 mL ultra pure water was brought into the vessel and the liquid was stirred at 400 rpm.

Second, the power dissipated to the liquid was calibrated for all transducers by calorimetry. The reactor was filled with 150 mL ultra pure water and insulated by fiberglass to avoid heat losses to the environment. Next, the temperature increase was recorded for 10 min at different input powers and the calorimetric power was calculated over these 10 min using Eq. (1) [27].

$$P_{cal} = \frac{dT}{dt} C_p m \quad (1)$$

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