Proceedings of Meetings on Acoustics

Volume 32 http://acousticalsociety.org/

2017 ICU Honolulu

Sixth International Congress on Ultrasonics

Honolulu, Hawaii, USA

18-20 December 2017

Physical Acoustics: Paper ICU2017 - 287

Elucidating the mechanism of paracetamol sonocrystallization for product purity enhancement

Clarissa Forbes

EPSRC Centre for Continuous Manufacturing and Crystallisation, Department of Chemical & Process Engineering, University of Strathclyde, Glasgow, UNITED KINGDOM; clarissa.forbes@strath.ac.uk

Thai T. H. Nguyen

School of Chemical & Process Engineering, University of Leeds, Leeds, England, UNITED KINGDOM; H.Nguyen1@leeds.ac.uk

Richard L. O'Leary

The Centre for Ultrasonic Engineering, Department of Electronic & Electrical Engineering, University of Strathclyde, Glasgow, Scotland, UNITED KINGDOM; richard.o-leary@strath.ac.uk

Chris J. Price

Chemical & Process Engineering, University of Strathclyde, Glasgow, Scotland, UNITED KINGDOM; chris.price@strath.ac.uk

We have previously demonstrated product purity enhancement during the crystallization of paracetamol in a low intensity ultrasound field. In order to elucidate the underlying mechanisms of sonocrystallization, the applied ultrasonic interventions were characterized by measurements of cavitation bubble number, size and size distribution with a Mettler FBRM probe. Ultrasonic intensity measurements were conducted using a needle hydrophone. The solvents selected for study; water, ethanol and isoamyl alcohol show significant differences in behavior. This data provides an insight into the relationship between solvent properties and cavitation bubble activity under the same applied ultrasonic energy. Substantially more cavitation bubbles form in the organic solvents compared with water, this is consistent with the lower surface tension and higher vapor pressure of the organic solvents. The difference in bubble size distributions between ethanol and isoamyl alcohol is significant. In ethanol most bubbles remain below 30μm whereas in isoamyl alcohol they tend towards 1mm in size. Detection, quantification and measurement of cavitation bubbles in crystallization solvents contributes further evidence that acoustic cavitation is a key component in sonocrystallization. The industrial driver is to incorporate this understanding into both pharmaceutical process and equipment design to improve the product quality, reduce waste and improve access to medicines.

INTRODUCTION

Crystallization is the predominant separation technique used to manufacture pharmaceutical products, whereby purification is achieved at the solution – lattice interface by molecular recognition. The predominant effect of sonocrystallization is through cavitation bubbles which are known to induce crystal nucleation.[1] Acoustic cavitation is the processes of nucleation, growth and collapse of bubbles consisting of vapor and dissolved gas generated from the passage of ultrasonic waves through a liquid. These events simultaneously create highly localized extremes of temperature and pressure, resulting in shockwave formation in the liquid.[2,3] Wohlgemuth *et al.* reported that a lower free energy barrier for nucleation is created at the surface of cavitation bubbles.[4] Nalajala *et al.* have also reported that shockwave formation increased the crystallization nucleation rate by an order of magnitude.[5] Therefore, both the effects of shockwave formation and heterogeneous nucleation are presumed to induce crystal nucleation.

We have previously demonstrated product purity enhancement during the crystallization of paracetamol in a low intensity ultrasound field.[6] The classic benefits such as accelerated nucleation, enhanced yield and reduced crystal size were also reported. In order to elucidate the underlying mechanisms, it is necessary to characterize the applied ultrasonic intervention. Quantification of bubble populations is fundamental to characterizing a cavitating ultrasonic field and hence to elucidating the underlying mechanisms of sonocrystallization. This work sets out to detect cavitation bubbles formed during sonication and investigate the effect of solvent properties on the bubble population. In a multi-bubble system, bubbles grow via rectified gas diffusion and coalescence phenomena, where the rate of coalescence is proportional to the square of the number density of bubbles.[7,8] In such a system the bubble-bubble interactions are known to suppress the bubble expansion.[9] Also, moving bubbles are reported to attenuate and scatter an acoustic wave. This is further complicated by the contribution from bubbles coalescing with each other and growing, alongside the formation of new bubbles.[7]

Iida *et al.* evaluated the sequential development of the bubble population by pulsed laser diffraction in a multi-bubble system, generated in a sonochemical reactor.[10] Surfactant concentration was shown to drastically affect bubble population; when the surfactant concentration increased, the bubble size became smaller and the number density of bubbles markedly increased. This was due to bubble coalescence being effectively suppressed by increasing amounts of the surfactant.[10] Kordylla *et al.* investigated the effect of ultrasound on the nucleation of dodecanedioic acid dissolved in acetonitrile, ethyl acetate, and propyl acetate and report that the nucleation behavior with ultrasound was similar, whereas in the absence of ultrasound the differences were more marked despite difference in solvent properties such as vapor pressure and surface tension.[11] This similarity in behavior may be linked to the cushioning effect described by Lorimer and Mason, in which cavitation effects are greatly reduced when large numbers of cavitation bubbles are generated simultaneously, reducing ultrasonic energy dissipation through the fluid.[12]

Lorimer and Mason also described how different solvent properties affected cavitation. In the case of solvents with high vapor pressure, cavitation is more readily generated during sonication, but less intense cavitational effects are observed as this causes a decrease in the maximum temperature attained on collapse and thus bubble implosion is less violent. Moreover, solvents with low surface tension are reported to exhibit lower cavitation thresholds and therefore it should be more energetically favorable to form bubbles. Conversely, due to the strong cohesive forces present in more viscous solvents, it is more energetically expensive to generate the large negative pressures required to form cavities in viscous solvents.[12] John *et al.* recently confirmed these general expectations, reporting enhancement of an ultrasound-assisted liquid-liquid extraction, by observing higher cavitational activity with lower viscosity, higher interfacial tension and higher vapor pressure solvent properties.[13]

MATERIALS AND METHODS

Both the ultrasonic intensity and bubble population measurements were carried out in deionized water (dispensed via Millipore Milli-Q water purification system), ethanol (VWR, ≥99.8% purity LOT:17H234022) and isoamyl alcohol (Alfa Aesar, 99% purity LOT:10200114). Physical property data for the solvents selected for this study are presented in Table 1. The experimental setup for our earlier paracetamol sonocrystallization experiments is shown in Figure 1. In the current work, the same double side arm, Wheaton© Celstir© 125ml vessel was filled with solvent

and placed onto a submersible Telesystem 15.20 stirrer plate (Thermo Scientific MA, USA) immersed in a XUB25 ultrasonic bath, (Grant Instruments, Royston, UK) operating at 35 ± 3 kHz.

Table 1. Solvent physical property data ([14,15])

Solvent Properties at 20°C	Water	Ethanol	Isoamyl alcohol
Density [g cm^{-3}]	0.9982	0.7893	0.8104
Viscosity [mPa·s]	1.002	1.200	3.692
Vapor Pressure [kPa]	2.34	5.95	3.73
Surface Tension [mN·m^{-1}]	72.86	22.39	24.09

Figure 1. Experimental setup for sonocrystallization experiments in the XUB25 ultrasonic bath

The sono-mechanical activity in the ultrasonic bath was characterized by measurement of acoustic intensity using a NH4000 PVDF needle hydrophone (Precision Acoustics Ltd., Dorset, UK, calibrated by the National Physical Laboratory, Teddington Middlesex UK). The time domain waveform from the hydrophone was recorded with an Agilent Technologies InfinniVision X2024-A digital oscilloscope (Agilent Technologies, South Queensferry, UK). As the PVDF hydrophone tip is incompatible with organic solvents, it was protected inside a DI water-filled latex-rubber sheath. A G400 Focused Beam Reflectance Measurement (FBRM) probe (Mettler Toledo, OH, USA) was used to detect and count cavitation bubbles generated by sonication. Each measurement consisted of acquiring chord length distributions for 60s of non-insonated (silent conditions), followed by 60s of sonication and subsequently 60s of silent conditions in order to generate the number of particle counts vs time data. The number of counts measured during sonication were totalled and subsequently assigned to user defined bubble size quanta ranging from <2µm-1000 µm. The needle hydrophone and FBRM probe were both positioned at the same height and aligned with the central axis of the crystallization vessel. Data was collected with the vessel located around defined positions on the stirrer plate at the bottom of the ultrasonic bath. In both cases, the measurements were averaged across the same four positions and carried out at 50% and 100% ultrasonic power settings available on the XUB 25 bath.

RESULTS AND DISCUSSION

The peak instantaneous intensities measured in DI water, ethanol and isoamyl alcohol are shown in Table 2. The local ultrasonic field in the XUB25 ultrasonic bath can be described as chaotic with intensities which vary substantially both with position and time. This complicates the comparison of measurements taken across the range of solvents under investigation. As noted earlier in instances where a large number of cavitation bubbles may be generated and bubble shielding effects can occur, see for example Nguyen *et al.*[16] Therefore, although a broadly similar magnitude of ultrasonic intensity can be inferred from this data, in solvents with a lower cavitation threshold a larger population of bubbles may be generated under the same magnitude of ultrasonic irradiation. The absorption and scattering of these bubbles will weaken this field. This results in a reduced level of ultrasonic energy being dissipated through the fluid. This is further compliated by bubble shielding effects at the hydrophone tip, the bubbles are more likely to form readily. Whilst lower acoustic intensity measurements are recorded under these conditions this is of limited value in characterization of the ultrasonic field in order to investigate the effect of solvent properties on cavitation bubble population.

Table 2. Measured ultrasonic intensities

	Average Intensity [mW cm^{-2}]	
Solvent	50% pov	100 % pov
DI Water	0.76 ± 0.55	3.33 ± 2.46
Ethanol	0.54 ± 0.40	4.03 ± 0.71
Isoamyl Alcohol	0.54 ± 0.10	3.71 ± 1.26

The FBRM data is presented in Figure 2 as the total number of counts measured over 60 seconds of ultrasonic irradiation across defined bubble size quanta, at 50% power and 100% power settings. The bubble number, size and size distributions measured in the three solvents are consistent across the solvents at the two powers however the bubble counts are significantly lower at the 50% power setting. A significantly lower number of cavitation bubbles

were measured in water, which has a much greater surface tension compared to the other two solvents. Linking low cavitation activity with high surface tension is consistent with it being more energetically expensive to nucleate bubbles in high surface tension solvents. At the 50% power setting, it is noticeable that the highest average intensity 0.76 ± 0.55 mW.cm^{-2} was measured in water, where very few bubbles were counted in the FBRM measurements. In the other solvents where the bubble count is higher there is the possibility of, bubble-bubble attenuation effects and hydrophone shielding occurring. In ethanol and isoamyl alcohol, where large numbers of cavitation bubbles are detected at both 50% and 100% power, effects that arise in multi-bubble systems are thought to influence the ultrasonic field by attenuating the ultrasonic energy dissipation and shielding the hydrophone surface.

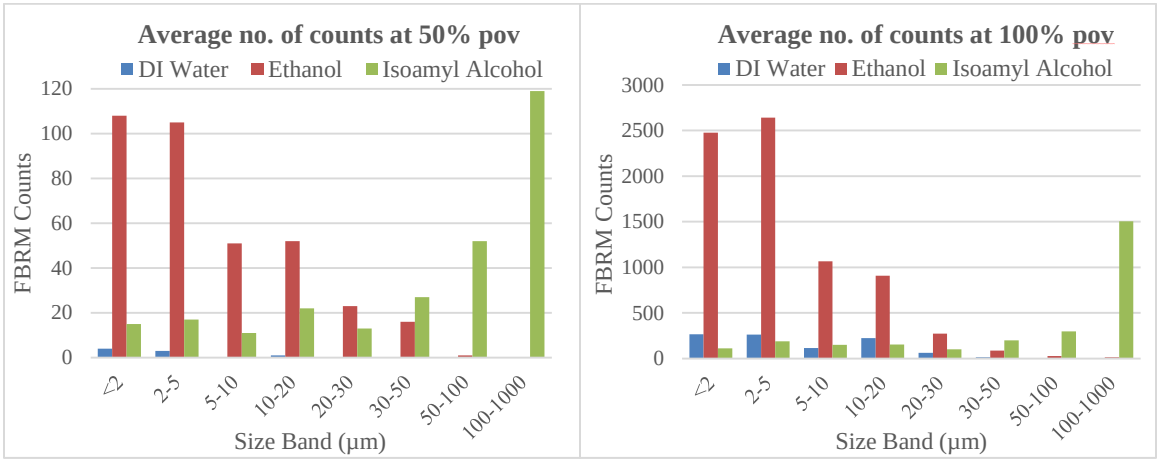

Figure 2. Average number of FBRM counts of bubbles generated during sonication at 50% power (left) and at 100% power (right)

The highest bubble counts were measured in ethanol at 100% applied power. Ethanol has a significantly higher vapor pressure than both water and isoamyl alcohol and therefore, bubbles are nucleated more readily during sonication. In the case where large numbers of cavitation bubbles are generated, less intense cavitation effects are observed.[13] Examining the bubble size and size distributions, proportionately more and smaller bubbles are generated in water and ethanol and generally, the bubbles detected in isoamyl alcohol are much larger and have a wider size distribution than those in water and ethanol. Isoamyl alcohol is significantly more viscous than ethanol and water and therefore, it may be more energetically expensive to generate the large negative pressures required to form bubbles in isoamyl alcohol, compared to the less viscous solvents. The strong cohesive forces present in the more viscous solvent may be contributing towards bubble coalescence. Brotchie *et al.* reported bubble coalescence as the main determinant of bubble size in an acoustic field.[17] As coalescence rates increase proportionally with the number of bubbles present, this may explain why this effect appears to be more pronounced in the case of isoamyl alcohol at 100% applied power, where there are substantially fewer bubble counts in smaller size bands, whereas there is a higher total population of smaller bubbles at the lower applied power. As bubble-bubble interactions are known to suppress the bubble expansion,[9] in the case of ethanol where these effects are thought to be the most severe, bubble coalescence is presumed to be suppressed here and therefore smaller bubble sizes are observed.

CONCLUSION

The focus of this research was to characterize the ultrasonic interventions that have been applied in previous sonocrystallization experiments.[6] The research objective was to quantify the cavitational activity in order elucidate the underlying mechanisms of sonocrystallization. The solvents selected for study; DI water, ethanol and isoamyl alcohol show significant differences in behavior. Average field intensity measurements made with the needle hydrophone in conditions where the cavitation intensity is high may be subject to errors associated with attenuating and shielding effects occurring in the multi-bubble field. However, this technique is well suited for the determination of the cavitation threshold in these solvents as the bubble population is modest at the cavitation threshold.

Measurements of cavitation bubble number, size and size distribution were conducted using a Mettler FBRM in the three solvents investigated. This data provides an insight into the relationship between solvent properties and

cavitation bubble activity under the same applied ultrasonic energy. Substantially more cavitation bubbles form in the organic solvents compared with water, this is consistent with the lower surface tension and higher vapor pressure of the organic solvents. The difference in bubble size distributions between ethanol and isoamyl alcohol is significant. In ethanol most bubbles remain below 30µm whereas in isoamyl alcohol they tend towards 1mm in size. Detection, quantification and measurement of cavitation bubbles in crystallization solvents contributes further evidence that acoustic cavitation is a key component in sonocrystallization - further work is planned to investigate this phenomenon. For example, measuring the cavitation threshold and quantifying the bubble population characteristics in the presence of dissolved solute molecules. This is a necessary step towards enhancing the current understanding the role of cavitation bubble activity in the sonocrystallization of pharmaceutical products from organic solutions. The ultimate aim of the research is to facilitate the design and optimization of industrial sonocrystallization processes.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the financial support of the EPSRC research grant EP/L014971/1, "Transforming industrial crystallization by sono-mechanical manipulation of crystal surfaces" the Department of Chemical and Process Engineering, University of Strathclyde; and both the EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC) National Facility laboratories, and the Centre for Ultrasonic Engineering (CUE) for access to laboratory facilities.

REFERENCES

1. Hem SL. The effect of ultrasonic vibrations on crystallization processes. Ultrasonics. 1967 Oct 1;5(4):202-7.

2. Suslick KS. The chemical effects of ultrasound. Scientific American. 1989 Feb 1;260(2):80-7.

3. Lauterborn W, Ohl CD. Cavitation bubble dynamics. Ultrasonics sonochemistry. 1997 Apr 1;4(2):65-75.

4. Wohlgemuth K, Kordylla A, Ruether F, Schembecker G. Experimental study of the effect of bubbles on nucleation during batch cooling crystallization. Chemical Engineering Science. 2009 Oct 1;64(19):4155-63.

5. Nalajala VS, Moholkar VS. Investigations in the physical mechanism of sonocrystallization. Ultrasonics Sonochemistry. 2011 Jan 1;18(1):345-55.

6. Nguyen TTH, Khan A, Bruce LM, Forbes C, O'Leary RL, Price CJ. The Effect of Ultrasound on the Crystallisation of Paracetamol in the Presence of Structurally Similar Impurities. Crystals. 2017 Sep 30;7(10):294.

7. Ashokkumar M, editor. Theoretical and experimental sonochemistry involving inorganic systems. Springer Science & Business Media; 2010 Oct 17.

8. Ashokkumar M. The characterization of acoustic cavitation bubbles–an overview. Ultrasonics sonochemistry. 2011 Jul 1;18(4):864-72.

9. Yasui K, Lee J, Tuziuti T, Towata A, Kozuka T, Iida Y. Influence of the bubble-bubble interaction on destruction of encapsulated microbubbles under ultrasound. The Journal of the Acoustical Society of America. 2009 Sep;126(3):973-82.

10. Iida Y, Ashokkumar M, Tuziuti T, Kozuka T, Yasui K, Towata A, Lee J. Bubble population phenomena in sonochemical reactor: I Estimation of bubble size distribution and its number density with pulsed sonication–Laser diffraction method. Ultrasonics sonochemistry. 2010 Feb 1;17(2):473-9.

11. Kordylla A, Koch S, Tumakaka F, Schembecker G. Towards an optimized crystallization with ultrasound: effect of solvent properties and ultrasonic process parameters. Journal of Crystal Growth. 2008 Aug 15;310(18):4177-84.

12. Lorimer JP, Mason TJ. Sonochemistry. Part 1—the physical aspects. Chemical Society Reviews. 1987;16:239-74.

13. John JJ, Kuhn S, Braeken L, Van Gerven T. Effect of fluid properties on ultrasound assisted liquid-liquid extraction in a microchannel. Ultrasonics Sonochemistry. 2018 Apr 30;42:68-75.

14. Smallwood I. Handbook of organic solvent properties. Butterworth-Heinemann; 2012 Dec 2.

15. Riddick JA, Bunger WB, Sakano TK. Organic solvents: physical properties and methods of purification.

16. Nguyen TT, Asakura Y, Okada N, Koda S, Yasuda K. Effect of ultrasonic cavitation on measurement of sound pressure using hydrophone. Japanese Journal of Applied Physics. 2017 Jun 13;56(7S1):07JE06.

17. Brotchie A, Statham T, Zhou M, Dharmarathne L, Grieser F, Ashokkumar M. Acoustic bubble sizes, coalescence, and sonochemical activity in aqueous electrolyte solutions saturated with different gases. Langmuir. 2010 Jul 1;26(15):12690-5.