

Quantifying Ultrasound for Sono-crystallization

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Abstract—The application of ultrasound to crystallization processes is a well-established technique employed to control the initiation of nucleation and therefore to achieve control over the crystal size and size distribution. In the context of Apfel's golden rules of cavitation: "Know thy liquid," "Know thy sound field" and "Know when something happens," the third rule has been satisfied. However, in order to link the applied ultrasonic energy to the enhanced process parameters, it is important to characterize the sound field and cavitation activity in the crystallization solvent. In order to better understand and design sono-crystallization experiments in the context of pharmaceutical manufacturing, measurements of acoustic emissions, broadband integrated voltage and focused beam reflectance measurements (FBRM) have been carried out in five typical crystallization solvents and water at a fundamental frequency of 40 kHz. The approaches taken have been to detect and measure cavitation activity as a function of ultrasonic power, allowing a comparison across the solvents.

Keywords—cavitation, acoustic emissions, broadband integrated voltage, crystallization solvents

I. INTRODUCTION

Acoustic cavitation is the process of nucleation, growth and collapse of bubbles consisting of vapor and dissolved gas generated from the passage of ultrasonic waves through a liquid. In 1933, Minnaert reported that the size of an oscillating bubble is inversely related to the frequency of its volume oscillations, and therefore at low ultrasonic frequencies, large bubbles are formed that produce large energies on collapse. [1] Acoustic emissions, such as harmonic, subharmonic and ultraharmonic frequencies of the ultrasonic driving frequency, are observed. In addition, broadband noise can be detected during cavitation events, which correspond to the bubble population (size and number) and the cavitation activity. In 1981, Apfel established golden rules on the topic of cavitation: "Know thy liquid," "Know thy sound field" and "Know when something happens." [2] Sonophysicist Crum expanded on these recommendations for sonochemists, emphasizing that accurate measurements of the sound field should be made and also that cavitation bubble dynamics are highly dependent on liquid vapor pressure and the dissolved gas concentration and composition.

In the sono-crystallization literature, Apfel's third rule has been satisfied. The application of ultrasound to influence the outcome of crystallization has been reported on many occasions [4,5] and shows particular benefits in the control of crystallization of pharmaceutical drug substances. The most widely reported application is controlled initiation of nucleation at supersaturation levels significantly below the conventional

metastable zone limit. A more recent application is to influence crystal purity by active removal of impurities during the crystal growth process [6] Jordens et al. studied the effect of ultrasonic frequency on the sono-crystallization of paracetamol in water and found that the most efficient frequency to improve nucleation was at 40 kHz. [7] This observation was rationalized as at larger frequencies the nucleation rate was lowered due to smaller bubbles being generated, which led to less violent implosions. Furthermore, it was suggested that there would be an optimum between the number and size of cavitation bubbles where the effect of the ultrasound was maximized.

From the perspective of a crystallization scientist, there are difficulties associated with satisfying Apfel's first and second rules as the vast majority of cavitation field and activity characterization work in the literature has been carried out in aqueous systems with measurement devices that are only compatible with water. At the National Physical Laboratory, Zeqiri et al. developed a novel acoustic cavitation sensor for monitoring acoustic emission spectra and characterizing cavitation activity by calculating the Broadband Integrated Voltage (BIV) [8,9]. BIV is calculated from the high frequency components of the broadband noise produced from cavitation bubbles. As shown in equation (1), the BIV is obtained by eliminating all fundamental, harmonic, subharmonic and ultraharmonic frequencies from the acquired spectrum. $V_s(f)$ represents the output voltage received from the hydrophone after these have been removed. $V_N(f)$ represents the output voltage of the background noise. f_s represents the integration start frequency and f_c corresponds to the stop frequency.

$$\text{BIV} = \int_{f_s}^{f_c} [V_s(f) - V_N(f)] df \quad (1)$$

Uchinda et al. reported that the BIV is less susceptible to the influence of nonlinear propagation of ultrasound in a study using the NPL cavitation sensor in order to relate the BIV to the dissolved oxygen content and sonochemical luminescence measured in water. [10]. 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 cavitation effects are observed. This causes a decrease in the maximum temperature attained on collapse and thus bubble implosion is less violent. Therefore, a lower BIV measurement, is expected for high vapor pressure solvents. [11]

II. EXPERIMENTAL METHOD

1-butanol ($\geq 99.5\%$), ethanol ($\geq 99.8\%$), isoamyl alcohol (IAA, $\geq 99.0\%$), and methyl ethyl ketone (MEK, $\geq 99.5\%$) were

purchased from VWR Chemicals (Lutterworth, UK). Acetonitrile (ACN, $\geq 99.5\%$) and ultrapure water (HPLC Grade) were purchased from Alfa Aesar (Heysham, UK). Prior to measurement, all solvents underwent a degassing process: involving sonication at 100% power at 50 °C for a duration of 30 minutes using a vacuum pump and a FB11211 bath (Fisher Scientific, Loughborough, UK). Physical property data for the solvents selected for this study are presented in Table 1.

TABLE I. SOLVENT PHYSICAL PROPERTY DATA [12]

Solvent Property	ACN	Butanol	Ethanol	IAA	MEK	Water
Surface tension (20°C mN/m)	29.1	24.6	22.3	23.8	24.6	72.8
Absolute viscosity (25°C cP)	0.38	3.00	1.08	4.20	0.41	0.89
Vapor pressure (21°C mmHg)	71.0	4.80	45.7	2.40	75.3	19.0

A schematic of the experimental setup for needle hydrophone and FBRM measurements is shown in Fig. 2. Measurements of acoustic emissions were carried out with a NH100 1.00mm PVDF needle hydrophone (Precision Acoustics Ltd., Dorset, UK), hydrophone calibration was provided by the National Physical Laboratory, (Teddington, UK). The time domain waveform from the hydrophone was recorded with an Agilent Technologies InfiniVision X2024-A digital oscilloscope (Agilent Technologies, South Queensferry, UK). As the PVDF hydrophone tip is incompatible with organic solvents, it was protected inside a castor oil-filled latex-rubber sheath ($d=5$ mm). The vessel was constructed by bonding a 250mL borosilicate glass beaker to a 40 kHz Tonpilz piezoelectric

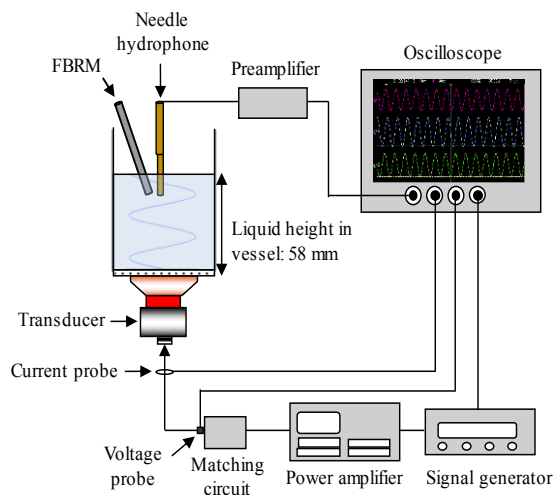


Fig. 1. Schematic of experimental setup for needle hydrophone and FBRM solvent measurements

transducer (CeramTec, Hampshire, England). The vessel was driven by a 33210A 10 MHz Function Generator (Agilent Technologies, South Queensferry, UK) and a wideband 155LCR power Amplifier (Kalmus Engineering, Rock Hill, SC). The hydrophone was mounted in a precision positioning stage (model: TVP-L, Sauter GmbH, Germany) and axially aligned with the Tonpilz transducer. A G400 Focused Beam Reflectance Measurement (FBRM) probe (Mettler Toledo, OH, USA) was used to detect and count cavitation bubbles generated by sonication. The probe was orientated 45° to the surface of the transducer, as recommended by the manufacturer. Each measurement consisted of acquiring chord length distributions at the various drive powers investigated for 30s of non-isonated (silent conditions), followed by 30s of sonication in order to generate the number of bubble counts vs time data. The number of counts measured during sonication were assigned to user defined bubble size quanta ranging from 1µm-1000 µm. Measurements of current and voltage allowed for electrical power to be determined. In this study, the drive powers under investigation were: 1, 3 and 5 W. Fast Fourier Transform signal processing using Matlab (Mathworks, Natick, MA, USA) was carried out in order to obtain the acoustic emission spectrum for each hydrophone measurement.

III. RESULTS AND DISCUSSION

By moving the hydrophone vertically upwards from close to the surface of the transducer at 0.01W electrical power drive, the standing waves were obtained and the antinodes were located as shown in Fig.2. For all subsequent hydrophone and FBRM measurements, the hydrophone was located 40mm from the bottom of the beaker. From the acoustic emission peak data obtained, there were no subharmonics or ultraharmonics in the case of all measurements carried out. Sharp emission peaks at the harmonics (f_2-f_7) were observed alongside simultaneous broadband peaks up to 4 MHz. An acquired frequency spectrum in the range 50-300 kHz is shown in Fig. 3. from a measurement in water at 1 W drive.

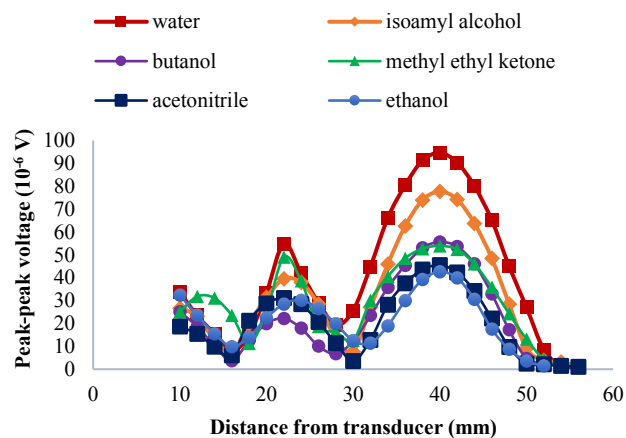


Fig. 2. Measured axial field response for the fundamental frequency of 40 kHz and 0.01 W.

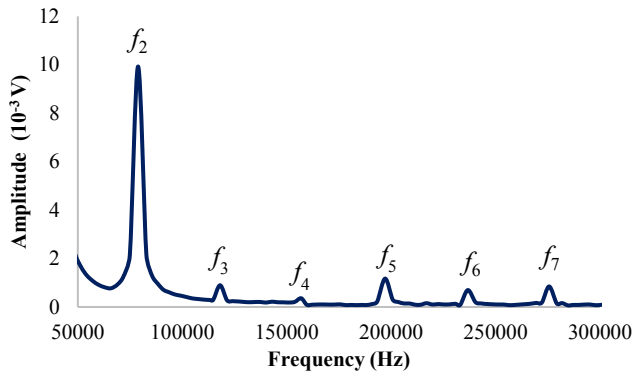


Fig. 3. Frequency spectrum acquired from measurement in water at 1 W

From earlier work carried out by Price et al. these spectral features strongly indicate the predominant occurrence of stable (or repetitive transient cavitation) [13]. Measurements of the sound pressures at the fundamental frequency, the BIV and FBRM bubble counting data for all solvents are shown in Table 2. During the measurements in water at 5 W, violent acoustic streaming was observed, and the largest BIV value was measured. Whereas in the case of the organic solvents, there was no violent streaming observed. Instead, large, inactive bubbles were observed during all organic solvent measurements. This was most severe in the case of isoamyl alcohol, where large clusters of bubbles were formed in the liquid. By considering the FBRM bubble counts in the range 20-150 μm , as a percentage of the total count across the organic solvents, there is a general agreement that a greater percentage of larger bubble counts corresponds to a larger BIV value.

From FBRM measurements, generally the number of bubbles increased with increasing sound pressure over the low power range investigated in this study. Across all solvents, zero counts were measured above 150 μm and in all cases, the vast

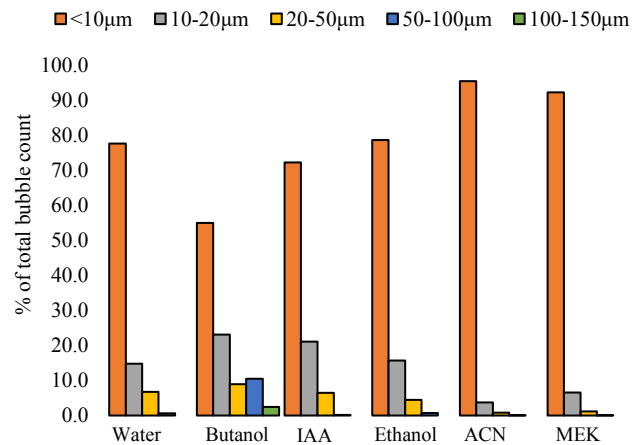


Fig. 4. FBRM bubble count at each size band as a percentage of total bubble count at 5 W

majority of bubble counts measured with FBRM correspond to $<10 \mu\text{m}$, which are likely to be bubble nuclei from previous cavitation events. In Fig. 4. the bubble counts at each size band are presented as a percentage of the total number of bubble range investigated in this study. Across all solvents, zero counts or each solvent, at 5 W. The lowest BIV values were measured in the highest vapor pressure solvents; MEK and ACN. Both of these solvents have the highest percentage of bubble counts $<10 \mu\text{m}$. This finding, along with the lower BIV values indicated a lower energy on collapse. A greater proportion of larger bubbles were measured in water, butanol, IAA and ethanol, which is in agreement with the higher BIV values obtained in these solvents at 5 W. The total sound pressure contribution from each of the harmonics in the range f_2 - f_7 , at 5 W, are shown in Fig 5. There was a marked difference between the measurements in water and the organic solvents, where an overall lower contribution from f_2 was observed. f_2 corresponds to the largest bubble size, which is in agreement with the lower BIV values measured in the organic solvents.

TABLE II. SOLVENT MEASUREMENTS OF THE SOUND PRESSURES AT THE FUNDAMENTAL FREQUENCY, BIV AND FBRM DATA

Power (W)	Sound Pressure at f_1 (Pa)			BIV [$\times 10^{-6}$ V \cdot Hz]			FBRM bubble counts in the range 20-150 μm as a % of total count		
	1	3	5	1	3	5	1	3	5
MEK	60927	74045	82696	60	143	189	2	1	1
ACN	58141	77206	84286	131	202	279	0	1	1
Ethanol	55034	78487	98479	135	170	318	8	5	5
IAA	56414	75561	90973	149	366	576	5	17	12
Butanol	57927	85210	100550	161	814	913	4	24	22
Water	33347	49497	61136	256	799	1794	11	12	10

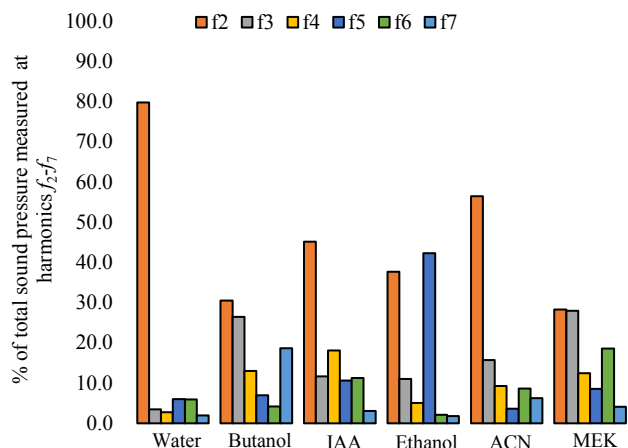


Fig. 5. The sound pressure from signals at harmonic frequencies are presented as a percentage of total sound pressure recorded at f_2-f_7 at 5W

IV. CONCLUSIONS

Measurements of the sound pressure contribution from harmonics and BIV were carried out with a needle hydrophone and bubble sizing was carried out with a FBRM probe over a low power range, across six solvents under the same applied electrical power. These measurements reveal marked differences between water and the organic solvents in this study, and in particular at 5 W drive power. Violent acoustic streaming was observed in water, which generated a greater proportion of larger bubbles compared to the organic solvents, corresponding to a higher BIV. From the FBRM bubble sizing in higher vapor pressure solvents, a larger proportion of smaller bubbles were generated and correspondingly lower BIV values were obtained.

FBRM is a widely used tool employed for tracking the evolution of the crystal size distribution during crystallization processes. From this work, it is apparent that it also provides a snapshot of cavitation activity and hence it can be used by crystallization scientists to monitor cavitation bubble size and number in the crystallization solvent for ultrasonic parameter optimization. A better understanding of the link between cavitation activity and desired process enhancements will help rationalize sono-crystallization experiments, especially in the absence of access to dedicated tools such as the needle hydrophone.

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