Supporting Information for

Sonofragmentation of Molecular Crystals

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1. Experimental Section

Materials and equipment. Dodecane (Reagent Plus, $\geq 99\%$), 1,10-dibromodecane (Fluka, $>95\%$), and glacial acetic acid (Fisher Scientific) were used as-received. Aspirin (acetylsalicylic acid, Aldrich, 99%) was recrystallized from acetic acid.

Sonications were performed at 20 kHz with a Sonics and Materials horn (VCX-750 for experiments at 10W or above, VCX-600 for experiments below 10W) with a 1 cm² diameter titanium horn. The sonicated solutions were thermostated with an Isotemp 1006S water bath. Ultrasonic intensities were calibrated by calorimetry with water.

Imaging and Analysis. Particles were imaged using a Canon PC1015 digital camera attached to a Zeiss Axioskop optical/fluorescence microscope with polarization analyzer and manually sized with the aid of a public-domain image processing program, ImageJ (available through NIH). The graphs presented in the main text are expressed in terms of particle volumes (with an assumption of an average spherical radius based on measured area of the micrograph projection); below we also provide equivalent figures based on measured particle area from the micrograph projection (i.e., for a rectangular particle, the area is simply the observed width times observed

length). Each data point represents the average of approximately 200 particles. Both methods of presentation lead to the same conclusions. Comparisons of particle volume emphasize the larger particles which are of greater interest because they represent the majority of the mass of the API.

Sonocrystallization of aspirin. The sonocrystallization procedure was adapted from a previously reported procedure.¹ In a typical experiment 6.71 g of aspirin were dissolved with stirring in 40.0 mL of acetic acid at 45 °C. The solution was supersaturated by cooling to 20 °C and the solution was sonicated at 10 W for 15 seconds to induce crystallization. Crystals were allowed to ripen for 24 hours and isolated by filtration and vacuum drying.

Sonofragmentation of aspirin. All sonication experiments apart from the initial crystallization were performed under a 20% duty cycle (i.e., a repeating cycle of 2 second ultrasound on, 8 second ultrasound off) in order to reduce temperature variation. During sonication, aliquots were removed by disposable pipette for analysis by optical microscopy. In all cases, sonications were done at low power (typically under 10 W as measured calorimetrically) and for short times to ensure that fragmentation was not taken beyond easily measured sizes during the times of the experiments.

Loading experiments were performed by suspending varying amounts of aspirin crystals in 5 mL dodecane followed by ultrasound treatment for 10 seconds total ultrasonic exposure at 5.5 W.

Particle-horn decoupling experiments were achieved by placing a slurry (0.08 g in 4 mL) in a 4 mL vial held directly below the horn with a flexible membrane (Figure 1a). The base of the vial had been cut off and replaced with a nitrile latex membrane to allow better penetration of the ultrasonic field while at the same time isolating the aspirin crystals from direct contact with the ultrasonic horn. Ethylene glycol was used as the coupling fluid outside the vial to provide for

transmission of the ultrasound from the horn into the vial contents. 1,10-dibromodecane was used as the suspending liquid in place of dodecane: the aspirin crystals were insoluble in both liquids, but due to its density 1,10-dibromodecane provided a much better suspension of the aspirin crystals without settling. The experiments were performed at 27 °C, the melting point of the 1,10-dibromodecane.

Particle-wall decoupling experiments used a latex membrane (Trojan™ non-lubricated condom, washed with water and ethanol and air-dried) placed around the slurry to protect particles from hitting the glass reactor wall (Figure 2b). A total of 8.0 mL of dodecane was required in order to adequately fill the membrane and the surrounding reaction cell, 3.0 mL between the membrane and the horn, the other 5.0 outside the membrane. 0.030 g aspirin was loaded into the membrane and compared to an experiment with 0.080 g aspirin in 8.0 mL of dodecane with no membrane.

The contribution of particle-wall and particle-horn collisions were additionally explored by employing sonication reactors of varying volumes, while holding the particle concentration constant at 0.01 g/mL and the horn immersion distance constant at 0.8 cm. Reactor cells with radii of 1, 1.5, 2, and 2.3 cm were used with corresponding liquid volumes of 5, 13, 27, and 30.5 mL of dodecane. Sonications were performed at 10 W for 30 seconds total ultrasonic exposure time.

2. Kinetics Derivation

The average particle size (S) is the total particle volume (V) divided by the total number of particles (N):

$$S = V/N \tag{S1}$$

The total particle volume is conserved while the total number of particles is the initial number of particles plus the number of additional particles formed by fragmentation:

$$N_{\text{total}} = N_{\text{initial}} + N_{\text{formed}} \quad (\text{S2})$$

The rate of particle breakage depends on the breakage mechanism. We will consider two cases: **(A)**, the assumption that the rate of particle breakage is dependent only on shockwave formation and therefore does not depend on interparticle collisions versus **(B)** the assumption that the rate of particle breakage is dominated by interparticle collisions and is therefore second order in particle concentration. Both cases assume that the number of cavitation events does not change and that mixing is equally efficient in all cases.

(A) Fragmentation model independent of interparticle collisions. If the particle breakage rate does not depend on interparticle collisions, then the particle formation rate (dN) can be described as a function of ultrasonic exposure time (dt) and a rate constant, k_1 , by a first-order differential equation.

$$dN = k_1 \cdot N \cdot dt \quad (\text{S3})$$

When integrated there is a linear relationship between the initial and final numbers of particles for a given ultrasonic exposure time (T).

$$N_{\text{final}} = N_{\text{initial}} \cdot e^{k_1 T} \quad (\text{S4})$$

Because V (the total volume of all particles) is constant, it can be expressed as the $S_{\text{initial}} \cdot N_{\text{initial}}$, so plugging equation 4 into equation 1 gives us a function for the average particle size (S) that is independent of loading:

$$S = S_{\text{initial}} \cdot e^{-k_1 T} \quad (\text{S5})$$

(B) Fragmentation model dominated by interparticle collisions. If the rate of particle breakage is dominated by interparticle collisions as the source of fragmentation, then it will be second order in particle concentration, and the rate equation depends on a different rate constant, k_2 , and integrates to equation 6.

$$1/N_{\text{initial}} - 1/N_{\text{final}} = k_2 \cdot T \quad (\text{S6})$$

Solving for N_{final} and inserting it into equation 1 gives the relationship shown in equation 7.

$$S = S_{\text{initial}} (1 - (N_{\text{initial}} \cdot k_2 \cdot T)) \quad (\text{S7})$$

3. Supplementary Plots

Figure S1. Effect of particle loading on final particle size (i.e., particle surface areas measured directly from optical micrographs) after sonication for 10 seconds at 5.5 W. For each mass loading, the solids were suspended in 5 mL of dodecane. The left most point is at 0.001 g mass loading.

Figure S2. Comparison of particle breakage between particles able to collide with ultrasonic horn (solid red line) and shielded from the horn (dashed black line). Horn output is 30 W.

Figure S3. Comparison of particle breakage between particles in a rigid container (solid red line) and in a flexible cell (dashed black line) for an ultrasonic exposure of 30 s.

Figure S4. Effect of changing reactor size on particle size after sonication. The reactor volume increases over a six-fold range and the ultrasonic horn to reactor wall distance changes from 1.0 to 2.4 cm. Particles were suspended in dodecane with a loading of 0.01 g/mL and sonicated for 30 seconds at 10 W.

References

- (1) Miyasaka, E.; Ebihara, S.; Hirasawa, I. *J. Cryst. Growth* **2006**, *295*, 97-101.