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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Sonofragmentation of Molecular Crystals

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Supporting Information

ABSTRACT: Possible mechanisms for the breakage of molecular crystals under high-intensity ultrasound were investigated using acetylsalicylic acid (aspirin) crystals as a model compound for active pharmaceutical ingredients. Surprisingly, kinetics experiments ruled out particle−particle collisions as a viable mechanism for sonofragmentation. Two other possible mechanisms (particle−horn and particle−wall collisions) were dismissed on the basis of decoupling experiments. Direct particle−shock wave interactions are therefore indicated as the primary mechanism of sonofragmentation of molecular crystals.

Developing processes for the production of active pharmaceutical ingredients (APIs) with a specific crystal size or polymorph distribution is critical for improved drug delivery by aerosolization, injection, or ingestion; for control of bioavailability; and for economy of preparation.[1,2] The use of ultrasound for the crystallization of APIs has attracted substantial recent attention[3−6] because of (1) its influence on particle size and size distribution,[7] (2) reduction of the metastable zone width, induction time, and supersaturation levels required for nucleation,[8−10] (3) improved reproducibility of crystallization,[11] (4) control of polymorphism,[12] and (5) reduction or elimination of the need for seed crystals or other foreign materials.[13]

Particle size distributions are very important in the preparation of APIs, as they are directly related to the dissolution rate and bioavailability. Adjustment of the particle size after crystallization by techniques such as grinding are often ineffective, are time- and energy-intensive, and can introduce impurities or defects.[14] Alternatively, the particle size can be influenced during crystallization by adjusting the number of nuclei formed in the initial stages of crystal growth: the more nuclei, the smaller the final crystals.[15] Ultrasound provides a facile method for controlling the number of nucleation sites created during crystallization.[16] The size distribution of the final crystals is a function of both the primary nucleation rate of the system (from disparity in ripening times among particles) and the rate of crystal fragmentation from sonication. An example of such sonofragmentation is shown in Figure 1.

The effects of ultrasound arise from acoustic cavitation: the formation, growth, and implosive collapse of bubbles coupled to the ultrasonic field. The rapid, nearly adiabatic implosion of a bubble results in intense local heating and high pressures (on the order of 5000 K and 1000 bar for multibubble cavitation) with heating and cooling rates >10^{10} K/s.[17,18] The collapsing bubble emits a shock wave that, in water, has pressures up to 60 kbar and velocities on the order of 4000 m/s.[19a] Cavitation at extended solid surfaces (i.e., ∼200 μm at 20 kHz) creates asymmetric bubble collapse, creating microjets that can cause pitting or generate shear forces.[19b,20] Enhanced mass transport, emulsification, and bulk heating also result, with often interesting chemical consequences.[20]

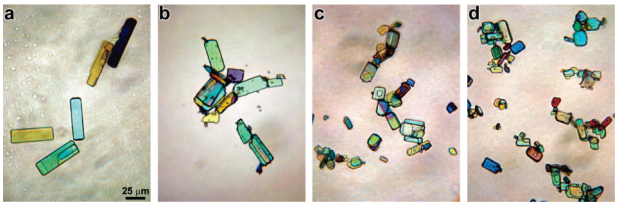

Figure 1. Cross-polarized optical micrographs showing the sonofragmentation of aspirin crystals (a) before sonication, (b) after 1 min of sonication, (c) after 3 min of sonication, and (d) after 10 min of sonication. Sonication at 10 W and 20 kHz was performed using a 1 cm^2 titanium horn immersed in a 2 wt % slurry in dodecane. All images were recorded at the same magnification.

Although there have been a variety of empirical investigations into the phenomenon of sonocrystallization, the nucleation mechanism remains poorly understood, and experimental reports have offered contradictory results. For example, high-speed photography has suggested that ice sonocrystallized from supercooled water is the result of pressure changes associated with emitted shock waves,[21,22] whereas other work has shown that bubbles can act as nucleation sites.[23] It has also been proposed that crystallization is expedited by increased supersaturation from diffusion of the API into heated liquid regions surrounding the collapsing bubble followed by rapid heat dissipation.[24]

Particle breakage after the initial crystallization event affects average particle sizes and size distributions both through reducing the size of existing crystals and by creating secondary nucleation sites. Although there is a thorough body of work on the effects of ultrasound on heterogeneous mixtures involving inorganic solids,[25−27] the literature on the effects of ultrasound on molecular crystals is modest. Experiments with metal particles conclusively showed the effects of interparticle collisions, which result in particle agglomeration, smoothing of surfaces, and removal of surface-passivating oxide coatings.[20d,26]

Fragmentation of molecular crystals during ultrasonic irradiation plays a central role in the process of sonocrystallization, and interparticle collisions are generally emphasized as the origin of such sonofragmentation.[28] However, the markedly different properties of molecular crystals in comparison with metallic particles (e.g., friability vs malleability, density, tensile strength,

Received: June 23, 2011

   dx.doi.org/10.1021/ja205867f | J. Am. Chem. Soc. XXXX, XXX, 000–000

melting point, etc.) should lead one to a closer examination of alternative possible mechanisms of fragmentation for molecular crystals. In fact, very early work in this area suggested that interparticle collisions are *not* important in the rates of particle breakage[29] or dispersion of aggregates,[30] although no effort was made to distinguish among other possible breakage mechanisms.

We suggest that there are four classes of possible mechanisms for sonofragmentation: interparticle collisions, horn−particle collisions, particle−wall collisions, and particle−shock wave interactions. Microjets from asymmetric bubble collapse are not expected at the surface of particles smaller than ~200 μm,[20d] but they could become significant contributors to fragmentation of larger particles. As described below, we ran a variety of experiments to differentiate among these possible mechanisms, and we conclude that interparticle collisions in fact are not a major contributor to particle breakage and that direct particle−shock wave interactions are implicated as the primary pathway.

Sonocrystallized aspirin suspended in dodecane (in which aspirin has no solubility) was used as a model system. Particle sizes were measured by direct image analysis of optical micrographs. The graphs presented here are expressed in terms of particle volumes, but in the Supporting Information (SI), equivalent figures based on particle area are presented (Figures S1−S4). Both methods of presentation lead to the same conclusions. The particle volume measurement emphasizes the larger particles, which are of greater interest because they represent the majority of the mass of the API.

The importance of interparticle collisions was evaluated by observing the effect of particle concentration on the final particle size. If the rate of particle fragmentation (dN/dt) were strictly first-order in particle concentration, then the average particle size (S) after a given ultrasonic exposure time (T) would be zeroth-order in the concentration of particles (i.e., N, the "loading" of the slurry, expressed as mass of solids per total volume) (eq 1):

$$S = S_{\text{initial}} e^{-k_1 T} \quad (1)$$

In contrast, if the rate of fragmentation were dominated by interparticle collisions, dN/dt would be second-order in N, and the particle size S would be linearly related to N (eq 2):

$$S = S_{\text{initial}}(1 - N_{\text{initial}} k_2 T) \quad (2)$$

In eqs 1 and 2, k_1 and k_2 are effective rate constants; derivations of these equations are provided in the SI.

Equation 2 is not quite correct because it assumes that the rate of breakage is independent of the particle size. In reality, the breakage rate at higher loadings of solids in the total volume (i.e., at larger N) would increase less dramatically than predicted because the breakage efficiency decreases as fragmentation occurs. We should, however, still expect a strong fragmentation-rate dependence on loading, especially for lower loadings. The observed effect of varying the number of initial particles (Figure 2) clearly shows essentially no dependence of the average particle size on loading: *interparticle collisions do not dominate the mechanism of sonofragmentation.*

There are three remaining possible mechanisms for sonofragmentation: particle−horn collisions, particle−wall collisions, and direct particle−shock wave interactions. High-speed photography has shown that particles can break through direct contact with the horn[29] and also that agglomerates can be dispersed directly by clouds of cavitating bubbles.[31] In order to determine which of these three proposed mechanisms dominates, experiments were performed to protect the particles from the wall or from the horn.

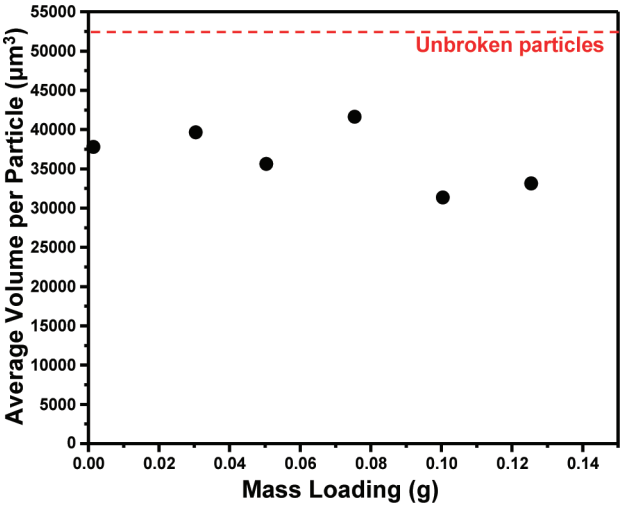

Figure 2. Effect of particle loading on final particle size after sonication for 10 s at 5.5 W. All masses were suspended in 5 mL of dodecane. The experimental error in the average volumes is estimated to be ±10%.

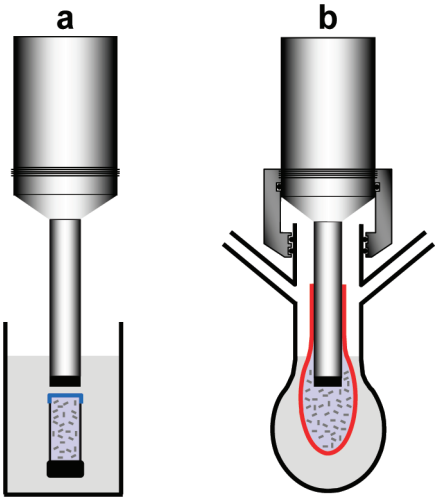

Figure 3. (a) Experimental setup for the particle−horn decoupling experiment. The vial contained a slurry of 1,10-dibromodecane and aspirin; outside the vial, ethylene glycol served as the carrier medium for the ultrasonic field, and a nitrile latex membrane (blue) separated the slurry from the carrier medium. (b) Experimental setup for the particle−wall decoupling experiment. A latex barrier (red) prevented particles from hitting the wall of the glass cell. The slurry was suspended in dodecane, and the space between the membrane and the reactor was filled with dodecane.

We eliminated particle−horn collisions by using a thin membrane to separate the slurry of aspirin from direct contact with the ultrasonic horn (Figure 3a; a detailed description is given in the SI). 1,10-Dibromodecane was used to slurry the aspirin powder both because it does not dissolve aspirin and because it has a good density match with aspirin (1.40 g/cm^3 for aspirin and 1.34 g/cm^3 for 1,10-dibromodecane vs 0.75 g/cm^3 for dodecane).

As shown in Figure 4, particles broke readily even in the absence of direct contact between the aspirin slurry and the

dx.doi.org/10.1021/ja205867f |J. Am. Chem. Soc. XXXX, XXX, 000–000

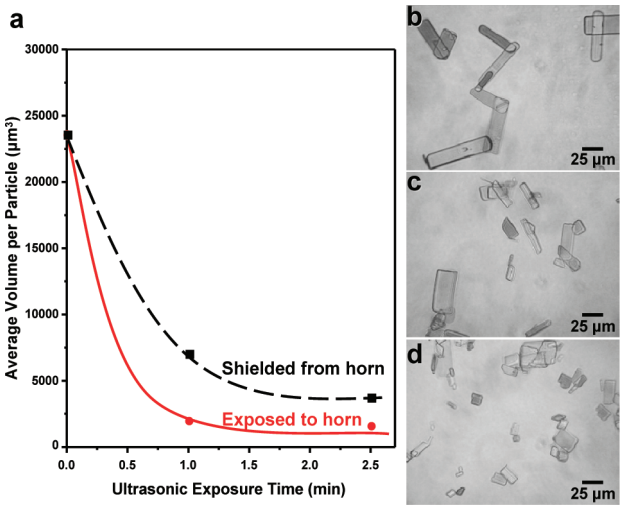

Figure 4. (a) Comparison of particle breakage when particles were able to collide directly with the ultrasonic horn (solid red line) vs when particles were exposed to ultrasound but shielded from direct contact with the horn (dashed black line). The horn output was 30 W. (b) Optical micrograph of particles before sonication. (c) Particles isolated from direct horn contact after 1 min of sonication. (d) Particles exposed to the horn after 1 min of sonication.

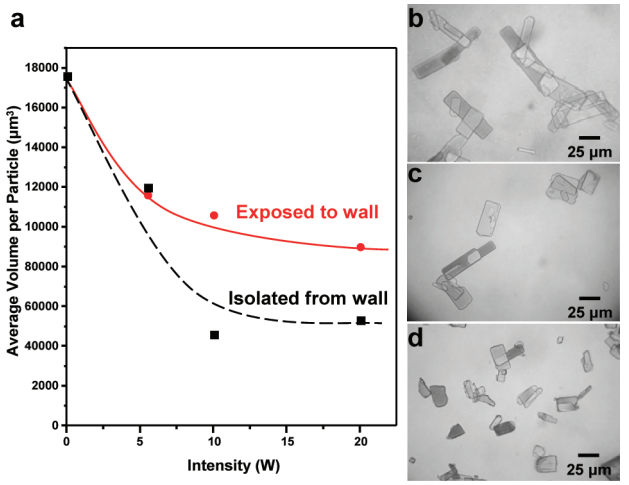

Figure 5. (a) Comparison of particle breakage for particles in a rigid container (solid red line) and particles in a flexible cell (dashed black line) after an ultrasonic exposure of 30 s. (b) Optical micrograph of particles before sonication. (c) Particles in the rigid container after sonication at 20 W for 30 s. (d) Particles in the flexible cell after sonication at 20 W for 30 s.

ultrasonic horn. The results of the comparable experiment of sonicating aspirin in 1,10-dibromodecane in a standard reactor are shown for reference, but a quantitative comparison has limited value because the membrane significantly attenuates the ultrasonic intensity and because there is a greater average distance between the slurry particles and the horn in the vial in comparison with direct horn immersion. Regardless, Figure 4 shows that particle−horn collisions are not the dominant mechanism of particle breakage.

We also showed that particle−wall collisions are not the primary breakage mechanism by using a flexible latex membrane

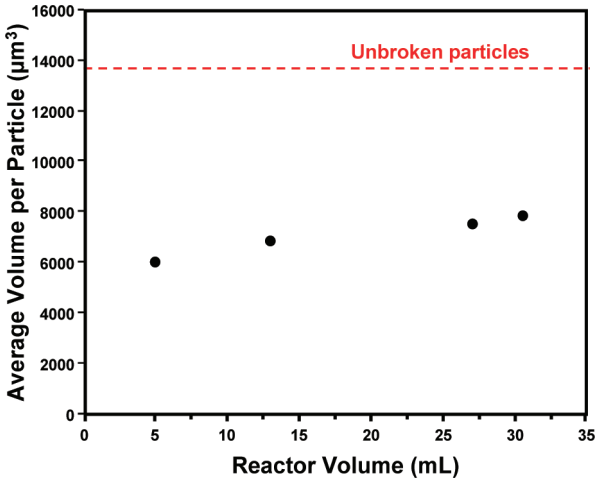

Figure 6. Effect of changing the reactor size on the particle size after sonication. The reactor volume was increased over a 6-fold range, and the distance between the ultrasonic horn and the reactor wall was changed from 1.0 to 2.4 cm. Particles were suspended in dodecane with a loading of 0.01 g/mL and sonicated for 30 s at 10 W.

to contain the slurry and prevent direct contact with the outer rigid glass reactor wall. This flexible cell was immersed in dodecane inside a glass container, as diagrammed in Figure 3b, so that acoustic reflection off the glass wall would still occur and the system would be perturbed as little as possible. The difference between particle breakage in the flexible cell versus the rigid-walled container is shown in Figure 5. The higher rate of breakage observed in the flexible cell is due to the closer proximity to the horn (and hence the cavitation zone) of the aspirin suspension within the membrane.

The insignificance of particle−wall and particle−horn collisions was further supported by varying the size of the reactor. Figure 6 shows that increasing the reactor size had only a modest effect (~30%) on the final particle size, even though the ratio of slurry volume to horn area increased by more than 6-fold and the distance from the horn to the reactor wall more than doubled. The minor change in final particle size is primarily due to dilution, since the size of the cavitation zone was constant.

In summary, particle-loading studies of molecular crystals have demonstrated that sonofragmentation is independent of slurry concentration, which rules out particle−particle collisions as an important breakage mechanism. This result is in stark contrast with metal powder slurries, where particle−particle collisions are predominantly responsible for the chemical and physical effects of sonication.[27] While there is little doubt that interparticle collisions do occur in slurries of molecular crystals irradiated with ultrasound, they are not the dominant source of fragmentation. In contrast to molecular crystals, metal particles are not damaged by shock waves directly and can be affected only by the more intense (but much rarer) interparticle collisions. The shift in dominant mechanisms for sonication of metal powders versus aspirin slurries highlights the differences in properties of malleable metallic particles and friable molecular crystals.

Of the remaining possible breakage mechanisms (particle−wall collisions, particle−horn collisions, and direct particle−shock wave interactions), decoupling experiments have shown that the first two possibilities are, at best, minor contributors to the total fragmentation rate. The dominance of direct particle−shock wave interactions has important implications for the design of

dx.doi.org/10.1021/ja205867f |J. Am. Chem. Soc. XXXX, XXX, 000–000

sonocrystallization processes and for ultrasonic processing of friable materials such as active pharmaceutical ingredients.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details, kinetics derivations, and supporting graphs. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We thank Richard D. Braatz and Michael L. Rasche for helpful discussions. This work was supported by the NSF (DMR 09-06904).

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