Sonofragmentation of molecular crystals: Observations and Modeling

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5aPA1. Sonofragmentation of molecular crystals: Observations and Modeling

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The need for new production methods of active pharmaceutical ingredients (APIs) with a specific crystal size distribution is acute for improved drug delivery by aerosolization, injection or ingestion, for control of bioavailability, and for economy of preparation. "Sonocrystallization" (i.e., the use of ultrasound for the crystallization of APIs) is under very active investigation for its ability to influence particle size and size distribution, reduce metastable zone-width, induction time, and supersaturation levels required for nucleation, improve reproducibility of crystallization, control of polymorphism, and reduce or eliminate the need for seed crystals or other foreign materials. We will review the potential mechanisms for the breakage of molecular crystals under high-intensity ultrasound and relate our experimental and modeling studies of the sonocrystallization and fragmentation of acetylsalicylic acid (aspirin) crystals as a model API. Surprisingly, kinetics experiments rule out particle-particle collisions as a viable mechanism for sonofragmentation. Direct particle-shockwave interactions are the primary mechanism of sonofragmentation of molecular crystals.

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INTRODUCTION

The need for new production methods of active pharmaceutical ingredients (APIs) with a specific crystal size distribution is acute for improved drug delivery (e.g., by aerosolization, injection or ingestion), for control of bioavailability, and for cost.[1-2] "Sonocrystallization" (i.e., the use of ultrasound for the crystallization of APIs) is under very active investigation for its ability to influence particle size and size distribution, reduce metastable zone-width, induction time, and supersaturation levels required for nucleation, improve reproducibility of crystallization, control of polymorphism, and reduce or eliminate the need for seed crystals or other foreign materials.[3-6]

While sonocrystallization has received considerable recent attention due to its ability to influence crystal properties for pharmaceutical applications,[3-13] reports on the effects of ultrasound on particles post-crystallization are surprisingly limited.[14] We will review the potential mechanisms for the breakage of molecular crystals under high-intensity ultrasound and relate our experimental and modeling studies of the sonocrystallization and fragmentation of acetylsalicylic acid (aspirin) crystals as a model API. Surprisingly, kinetics experiments rule out particle-particle collisions as a viable mechanism for sonofragmentation. Direct particle-shockwave interactions are the primary mechanism of sonofragmentation of molecular crystals.

The chemical and physical effects of ultrasound arise primarily 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 multi-bubble cavitation — with heating and cooling rates $>10^{10}$ K/sec.[15] The collapsing bubble emits a shockwave that, in water, has pressures up to 60 kbar and velocities on the order of 4000 m/sec.[16] Cavitation at extended solid surfaces (i.e., ~200 μm at 20 kHz) will create asymmetric bubble collapse, creating microjets that can cause pitting or generate shear forces.[16-17] Enhanced mass transport, emulsification, and bulk heating also result with often interesting chemical consequences.[17] There is a substantial body of work on the effects of ultrasound on heterogeneous mixtures involving inorganic solids,[17-20] and interparticle collisions with metal particles result in particle agglomeration, smoothing of surfaces, and removal of surface-passivating oxide coatings.[17def,20]

EXPERIMENTAL PROCEDURES

Aspirin crystals suspended in dodecane (in which aspirin has no solubility) was used as a model API sonocrystallization and sonofragmentation system: aspirin is inexpensive, relatively non-toxic, and it is relatively easy to prepare with crystals that are relatively uniform in size and of sufficient size for facile characterization by optical microscopy. Particle sizes were measured by direct image analysis of optical micrographs. The graphs presented here are expressed in terms of particle volumes. The particle volume measurement emphasizes the larger particles, which are of greater interest because they represent the majority of the mass of the API.

Materials and equipment. Dodecane (Reagent Plus, ≥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 cm^2 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). Each data point represents the average of approximately 200 particles.

Sonocrystallization of aspirin. 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. These were used as the starting material for our sonofragmentation studies.

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 (<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.

RESULTS AND DISCUSSION

The use of grinding, as an example, to adjust the particle size of APIs after crystallization is often ineffective and requires time and significant energy input. In addition, grinding can introduce impurities or defects. Alternatively, 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. Ultrasound provides a facile method to control the number of nucleation sites created during crystallization. The size distribution of the final crystals is a function both of the primary nucleation rate of the system (from disparity in ripening times among particles) and of the rate of crystal fragmentation from sonication. An example of such sonofragmentation is shown in Figure 1.

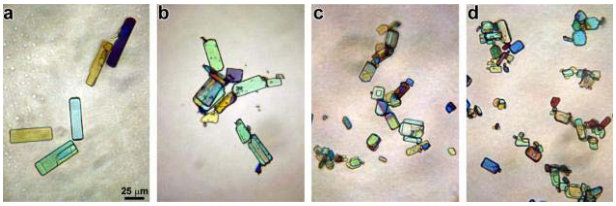

FIGURE 1. Sonofragmentation of aspirin crystals shown by cross-polarized optical micrographs; (a) before sonication, (b) after 1 min sonication, (c) after 3 min sonication, and (d) after 10 min sonication. Sonication using a 1 cm^2 titanium horn immersed in a 2 wt.% slurry in dodecane, 10 W, 20 kHz. All images at the same magnification; size bar given in (a).

In the process of sonocrystallization, fragmentation of molecular crystals during sonication plays a central role, and interparticle collisions are generally emphasized as the origin of such sonofragmentation.[21] The markedly different properties of molecular crystals compared to metallic particles (e.g., friability vs. malleability, density, tensile strength, melting point, etc.), however, should lead one to closer examination of alternative possible mechanisms of fragmentation for molecular crystals. One may divide the possible mechanisms for sonofragmentation into four classes: interparticle collisions, horn-particle collisions, particle-wall collisions, or particle-shockwave interactions. Microjets from asymmetric bubble collapse are not expected at the surface of particles below ~200 μm,[20] but they could become significant contributors to fragmentation of larger particles. As illustrated in Figure 2, we have run 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-shockwave interactions are implicated as the primary pathway.

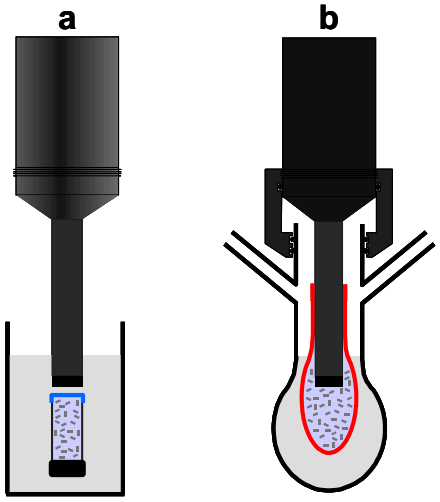

Figure 2. To determine the relative contributions of the four likely mechanisms of sonofragmentation (inter-particle collisions, horn-particle collisions, horn-wall collisions, and shockwave/turbulent shear, decoupling experiments were designed, as shown in above: (a) Using a vial contains a slurry of 1,10-dibromodecane and aspirin, the ultrasonic horn was decoupled from contact with the aspirin slurry particles; outside of the vial, ethylene glycol serves as the carrier medium for the ultrasonic field, and a nitrile latex membrane (blue) separates the slurry from the carrier medium. (b) Particle-wall decoupling experiment. A latex barrier (red) prevents particles from hitting the glass cell wall. The slurry is suspended in dodecane, and the space between the membrane and the reactor is filled with dodecane.

In order to examine the importance of interparticle collisions, we evaluated the effect of particle concentration on rates of sonofragmentation (e.g., final particle size after sonication for a fixed time at a fixed intensity). If the rate of particle fragmentation were strictly first order in particle concentration, then the average particle size after a given ultrasonic exposure time would be zero order in concentration of particles. On the other hand, if the rate of fragmentation were dominated by interparticle collisions, the rate of fragmentation would be second order in particle concentration, and the particle size would be linearly related to the initial particle concentration (i.e., mass loading in a slurry). As shown in Figure 3, there is essentially no dependence of average particle size after fragmentation on the mass loading (i.e., initial particle concentration): *interparticle collisions do not dominate the mechanism of sonofragmentation.*

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.[18-20] 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 shockwaves directly, and only can be affected by the more intense (but much rarer) interparticle collisions. The shift in dominant mechanisms between sonication of metal powders vs. aspirin slurries highlights the differences in properties between malleable metallic particles and friable molecular crystals.

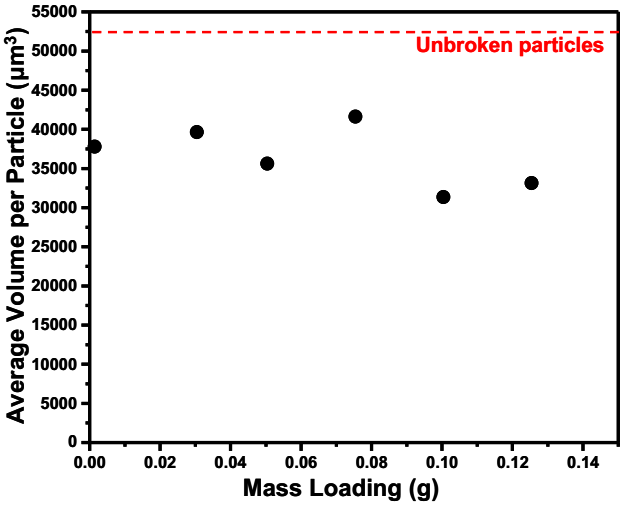

Figure 3. Interparticle collisions do not dominate sonofragmentation. Increasing the concentration particles in the slurry (mass loading) has no significant effect on the final particle size after sonication for 10 seconds at 5.5 W. All masses are suspended in 5 mL of dodecane. Experimental error of the average volumes are estimated to be ±10%.

Two other possible mechanisms for sonofragmentation (particle-horn collisions and particle-wall collisions) were eliminated as major contributors by the use of decoupling experiments, shown in Figure 2 (a) and (b), both of which show significant fragmentation.[14] We therefore reach the conclusion that the dominant mechanism of sonofragmentation is direct particle-shockwave and related particle-turbulent shear interactions. This mechanism has important implications for the design of sonocrystallization processes, for the optimization of the resulting slurry, and for ultrasonic processing of slurries of friable materials such as active pharmaceutical ingredients.

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