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Acoustic levitation: recent developments and emerging opportunities in biomaterials research

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Abstract Containerless sample environments (levitation) are useful for study of nucleation, supercooling, and vitrification and for synthesis of new materials, often with non-equilibrium structures. Elimination of extrinsic nucleation by container walls extends access to supercooled and supersaturated liquids under high-purity conditions. Acoustic levitation is well suited to the study of liquids including aqueous solutions, organics, soft materials, polymers, and pharmaceuticals at around room temperature. This article briefly reviews recent developments and applications of acoustic levitation in materials R&D. Examples of experiments yielding amorphous pharmaceutical materials are presented. The implementation and results of experiments on supercooled and supersaturated liquids using an acoustic levitator at a high-energy X-ray beamline are described.

Keywords Amorphous · Glass · Containerless processing · Pharmaceutical · API

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Introduction

The functional behavior and characteristics of biomaterials and pharmaceuticals depend on their structure (Patani and LaVoie 1996). Containerless methods provide a means of access to supercooled liquids and supersaturated solutions under well-controlled conditions. Using containerless methods enables the synthesis of non-equilibrium forms of materials, often with novel structures. These methods have been widely used to investigate high-temperature melts and to make glasses and non-equilibrium phases that cannot be made by other means (Price 2010; Kohara et al. 2004). Recent developments in acoustic levitation enable containerless experiments on low-temperature supersaturated solutions and supercooled liquids made from organic and pharmaceutical compounds.

For pharmaceuticals, it is essential that the active pharmaceutical ingredient (API) is absorbed and available in the body tissue where it is utilized. Poor absorption of the API reduces the efficacy of medications and may lead to contamination of the environment and food chain. Significantly increased solubility, faster dissolution, and higher bioavailability are generally observed for amorphous forms of pharmaceuticals than for their crystalline counterparts (Law et al. 2004; Yu 2001; Willart and Descamps 2008; Atassi et al. 2010; Lu and Rohani 2009; Kawakami 2009). Some pharmaceutical compounds are already made in amorphous forms. They are processed by methods such as melt quenching in containers, freeze and spray drying, milling, wet granulation, melt extrusion, and drying solvated crystals (Yu 2001; Willart and Descamps 2008). Some emerging pharmaceuticals cannot be effectively made amorphous by use of established methods.

Acoustic levitation can be used to suspend and manipulate liquid drops and solid particles without any contact

for a variety of analytical applications (De Castro and Capote 2007). Interest in the applied development of acoustic levitation/positioning was stimulated by the requirements of materials and fluid physics experiments for research under low gravity (Rindone 1982). Barmatz et al. (1985) developed resonant acoustic cavities to create regions that can trap small samples. Interference acoustic levitators were pioneered by Whymark (1975) and Rey et al. (1987) and further developed in the US (Trinh 1985), Europe (Lierke et al. 1983), and Asia (Xie and Wei 2001). Simple interference levitators comprise a single transducer and an opposed reflector. Shaping of the transducer radiator and/or the reflector can focus the sound field to produce a stronger radial restoring force (Rey et al. 1987). The transducer–reflector arrangement enables stable levitation but it does not enable manipulation of the sample. Single-axis levitators that use two opposed transducers can precisely control sample position. This is accomplished by controlling the relative acoustic phase of the drive signals to move levitated samples axially between the transducers (Weber et al. 2009). In addition, drops can be oscillated to enable the investigation of fluid dynamic properties or to mix multi-phase compositions (Trinh 1985; Weber et al. 2009). The main objective of this study was to investigate the solidification behavior of various substances suspended in an acoustic levitator, by using a high-energy X-ray beam to monitor the systems.

Single axis transducer–reflector acoustic levitators have been used in research on a variety of bio and pharmaceutical materials. In most cases, combining the levitation with a non-contact probe of the materials properties has been fruitful. Leiterer et al. (2008) combined acoustic levitation with fluorescence spectroscopy. They used laser-induced fluorescence to monitor solute concentration as the solvent was evaporated from solutions under containerless conditions. Leiterer et al. (2008) also investigated structural evolution during crystallization of aspirin, vitamin C, and other materials from concentrated solutions. Progress of the crystallization process was followed in situ by use of X-ray diffraction.

Acoustic levitation has been used extensively to investigate the production of high-quality large-molecular-weight protein crystals (Santesson et al. 2003). Knutsson (2006) worked to optimize a transducer–reflector levitator for use in the growth of protein crystals. Particular care was paid to methods of introducing and recovering samples from the levitator. Chung and Trinh (1998) used a hybrid acoustic-electrostatic levitator to produce lysozyme and thaumatin crystals from drops of precursor solutions. Puskar et al. (2007) extended the use of levitation to the study of respiration in living cells. They levitated small (5 μl) drops of red blood cells suspended in a host fluid and studied the heme dynamics in the cells by use of Raman spectroscopy. Respiration processes were compared in healthy cells and those infected with malaria.

Containerless methods are suitable for investigation of non-equilibrium phenomena. Neuefeind et al. (2011) used acoustic levitation in combination with in-situ X-ray diffraction to investigate the structure of supercooled water and deuterium oxide. They determined the structure and compared it with competing models of the effects of hydrogen bonding in the supercooled liquids.

More recently, the quest for amorphous forms of pharmaceutical materials has led to the application or acoustic levitation. Drynetics uses detailed models to optimize spray-drying processes. This organization uses acoustic levitation to investigate the effects of processing conditions when the amorphous forms of drugs are prepared (http://www.niro.com/niro/cmsdoc.nsf/webdoc/webb7ptc4r Drynetics). Benmore and Weber (2011) applied acoustic levitation combined with in-situ high-energy X-ray diffraction to investigate solution and melt phase processing of low-molecular-weight pharmaceuticals. The results indicate that formation of glassy and amorphous phases is significantly more favored in the containerless environment.

Acoustic levitation methods are an emerging tool that can be used, particularly in combination with non-contact diagnostic probes, to investigate new synthetic methods, materials properties, and bio-response.

Methods

Experiments were performed on organic and inorganic materials using acoustic levitation. The levitator comprised two acoustic transducers mounted vertically on a rigid post and separated by a distance of $\sim$15 cm. The transducers were excited with a $\sim$22 kHz sine wave drive current from a power supply. The power supply could be used to control both acoustic amplitude and the relative phase of the drive signals to each transducer (additional details are given by Weber et al. 2009). The levitator produces several nodes where samples can be located. In most cases, a single sample was placed in the central node located equidistant between the two transducers. Up to seven samples could be introduced into adjacent nodes separated by distances of $\sim$0.7 cm. Multiple samples were used in some experiments.

Three types of experiment were performed:

1. supersaturation of solutions by evaporating some of the solvent;
2. supercooling of liquids; and
3. in situ adjustment of the pH of solutions.

Several experiments were performed with the levitator installed at a high-energy X-ray beamline to make in-situ measurements of sample structure under controlled conditions.

Supersaturated solutions

Saturated solutions of pharmaceutical compounds were prepared by adding high-purity powdered material to a solvent contained in a glass vial. The solvents used were pure anhydrous ethanol and acetone. Materials investigated include: carbamazepine, cinnarizine, clofoctol, clotrimazole, dibucaine, ibuprofen, and probucol (Sigma–Aldrich, St Louis, MO, USA). The vial was agitated in an ultrasonic mixing bath and solute was added until no more would dissolve. The solution was then filtered to remove undissolved solids. Weighed samples of each solution were dried to determine the solute concentration.

Droplets were introduced into the levitator by use of a 1 cm^3 syringe. The syringe cannula was placed in the levitation node and a small volume of liquid was introduced. The solvent evaporated and the drop diameter decreased as the solution became supersaturated. Processed samples were recovered by placing a clean aluminium foil weighing boat under the levitation position. In some cases, the weighing boat was filled with liquid nitrogen to quench the sample as it was recovered. When the levitator was set up at the beamline, changes in the structure could be monitored by making a sequence of X-ray structure factor measurements during the solvent-evaporation process.

Supercooled liquids

Organic pharmaceutical materials were processed by heating them with the beam from a 10-Watt CO_2 laser (Synrad, Mukilteo, WA, USA; model J48-1S). Powdered starting material was placed on a copper plate and fused into 4–5 mm diameter boules by heating it with the unfocussed laser beam. The boules were cut into 2–3 mm chunks that were levitated. Materials that were investigated include: carbamazepine, cinnarizine, clofoctol, clotrimazole, dibucaine, and probucol. A chunk of material was introduced into the levitator by means of a wire-mesh spoon. The levitated sample was heated by slowly increasing the incident laser beam power. When the sample was completely molten, it was cooled either by reducing the laser power or moving it out of the heating beam by adjusting the acoustic controls. Samples were recovered by means of a wire mesh spoon or by catching them on a metal weighing dish. The samples were stored in a refrigerator until analysis by high-energy X-ray diffraction.

Water and deuterium oxide drops were cooled below ambient temperature by flowing cooled nitrogen across the levitated sample. The gas was supplied from a Cryostream Plus with a modified heating system (Weber et al. 2009; Neuefeind et al. 2011). The Cryostream was set to a temperature of −40°C and the heater was energized to warm the gas stream to approximately −15°C. A water drop was introduced into the levitation node and cooled to a temperature of approximately −15°C where it was stable for an extended period of time. The beamline hutch was closed and the X-ray beam was energized. The sample was then deeply supercooled by reducing the heater power and X-ray data were acquired from the supercooled liquid before it crystallized.

In-situ control of solution pH

pH control can be used to affect the solubility of materials. Experiments were performed on protonated calcium phosphate solutions that were made alkaline by addition of ammonia via the gas phase (J.B. Parise et al., unpublished research). Hydroxyapatite was dissolved in concentrated phosphoric acid and ammonia fumes were entrained in the gas around a levitated drop of the solution. The ensuing precipitation reaction was followed by acquiring video images of the levitated drop.

X-ray structure measurements

X-ray measurements were performed at beamline 11 ID-C at the Advanced Photon Source. The arrangement of the instrument is illustrated in Fig. 1. The acoustic levitator was installed by bolting it to a high-capacity X–Y–Z stage located upstream of the port where the X-ray entered the beamline hutch. The set-up was arranged so that the 1 × 1 mm X-ray beam was incident precisely at the location of the levitated sample. A tungsten rod was used to block the direct beam. Scattered X-rays were detected using a Perkin–Elmer model 1,621 amorphous silicon large-area detector that was located approximately 40 cm from the sample position. Using the 115 keV X-ray energy this arrangement enabled measurements over a Q value range of $\sim$0–20 $Å^{-1}$.

The X-ray data were acquired by computer and analyzed by use of software developed for this purpose (Hammersley et al. 1996; Qiu et al. 2004). The X-ray pair distribution functions were obtained from a sine–Fourier transformation of the S(Q), truncated at $Q_{max} = 25$ $Å^{-1}$ using a Lorch modification function (Lorch 1969) to reduce Fourier artifacts.

Results

Drops of water and pharmaceutical solutions in ethanol and acetone were stably levitated. Water drops up to $\sim$3.5 mm in diameter could be held until they evaporated to $\sim$0.5 mm diameter where they became unstable. Ethanol and acetone-based solutions could be levitated in sizes up to $\sim$2.5 mm in diameter. The organic solvents evaporated

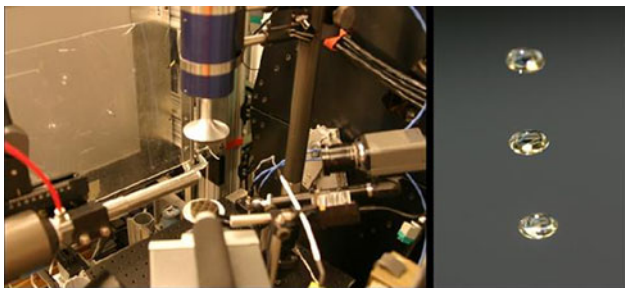

Fig. 1 *Left*, photograph showing the installation of the acoustic levitator at beamline 11 ID-C at the advanced photon source. The image shows the large-area X-ray detector to the far left, the Cryostream, acoustic levitator transducers with sound absorbing foam pads installed, video camera, and Inframetrics model 760 thermal imaging camera near the bottom center. *Right*, three levitated water drops. The drops are approximately 3 mm in diameter and are slightly flattened by the acoustic forces

rapidly at room temperature—a 2.5 mm diameter drop of pure acetone evaporated in approximately 2 min. Drops could be compressed by increasing the acoustic forces. Eventually, continued increase in the force resulted in atomization of the drop. Modulation of the acoustic forces caused oscillation of the drop. When the stimulation frequency matched the natural resonant frequency of the drop, it underwent large amplitude oscillations. Control of the relative phases of the drive current to the transducers was used to move samples vertically. An example of several drops levitated simultaneously is shown on the right of Fig. 1.

Saturated solutions of pharmaceutical materials were evaporated in the levitator. In some cases, as the solvent evaporated crystals formed from the concentrated solution. In several cases, crystallization was not detected by high-energy X-ray diffraction and the samples were recovered as viscous liquids. The example of probucol dissolved in acetone is shown in Fig. 2a. The products were usually stable at room temperature. For several of the materials made into gels, the calorimetric glass transition temperature (T_g) measured for glasses made from a melt was below room temperature (Baird et al. 2010). Several compositions were captured in a dish of liquid nitrogen that rapidly cooled the gel to a temperature considerably below T_g. The sample was quickly placed back into the levitator and its structure measured as it warmed up to room temperature. These measurements confirmed that the material was amorphous both above and below T_g.

Generation of amorphous pharmaceutical materials was also investigated by melting levitated samples. The laser beam power required to melt the samples was in the range 15–25% (1.5–2.5 Watts) for most compositions. Carbamazepine required approximately 50% (5 Watts) of laser power to completely melt the sample. From previous experience with laser beam heating, we estimate that approximately 25% of the laser beam power was absorbed by the sample. When the samples were heated, they developed instabilities. These were mainly radial oscillations ca. ±2 mm in magnitude or spinning of the liquid drop. The spinning drops formed a flattened "pancake" shape and required greater acoustic power to levitate than did the starting solid. Despite these instabilities, drops of a variety of materials could be processed and recovered. The diffraction patterns of the drugs processed in this manner were compared with the same starting materials gently heated with the laser beam in a copper hearth.

X-ray structure data for a carbamazepine sample made from a levitated melt is shown in Fig. 2b. The data for the crystalline starting material are also shown in the figure. Additional examples of data obtained from levitated samples are presented in Benmore and Weber (2011).

In the experiments to supercool water, considerable care was needed to align the Cryostream jet with the sample. If the gas flow rate was more than approximately 2 l min^{-1},

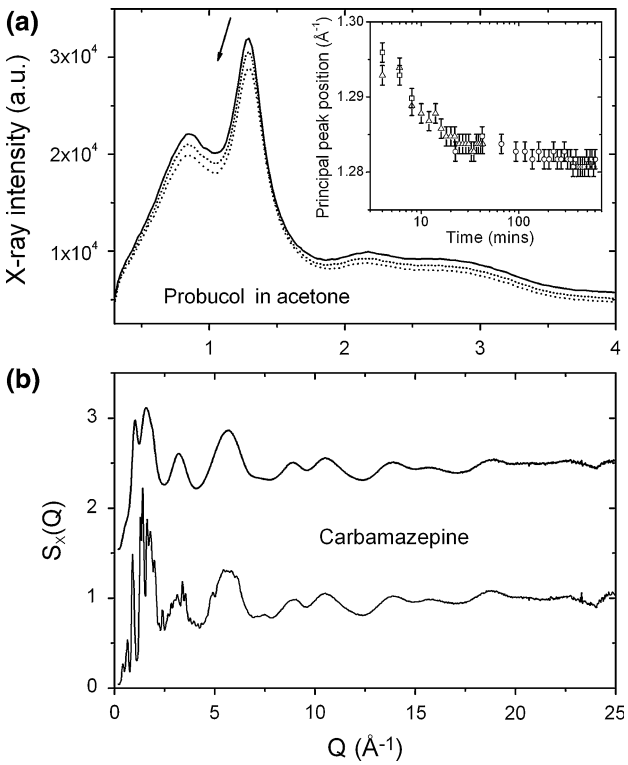

Fig. 2 **a** The background-corrected X-ray intensity from a levitated saturated droplet of the cholesterol-reducing drug probucol, dissolved in acetone over time; after 4 min (*solid line*), 8 min (*dotted line*), and 44 min (*dashed line*). The *inset* shows the evolution of the position of the principal peak in the X-ray signal over time as the acetone evaporates to leave a viscous gel. The *different symbols* represent measurements on different droplets. **b** Comparison of the measured X-ray structure factors for the mood-stabilizing drug carbamazepine. *Top*: amorphous material prepared by cooling a levitated molten drop. *Bottom*: crystallized material prepared by melting and cooling in a container

the drop was displaced from the acoustic node and levitation became unstable and sometimes failed. Water and D_2O drops were supercooled to approximately −20°C by levitating them at higher temperatures and then rapidly cooling them by reducing the power to the gas stream heater. At the lowest temperatures, the supercooled liquid state existed long enough (approx. 20 s) to make a structure factor measurement before it crystallized. Structure factor measurements were made over a range of temperatures from approximately +20 to −20°C. The results were compared with the TIP4 and TIP5 models for the structural changes that occur during supercooling. The conclusion is that the TIP4 model provides a more reliable interatomic potential for describing the temperature dependence of the structure of liquid water (Neuefeind et al. 2011).

Discussion

The ability to extend the range of amorphous materials that can be generated is useful in many aspects of materials research, including optical materials and fiber optics, metallic glasses, and pharmaceuticals. It is especially useful in developing new drug treatments from emerging compounds that have very limited solubility in the crystalline form. Processing concentrated solutions of low-molecular-weight compounds resulted in viscous liquids with no evidence of crystallinity when probed with a high-flux, high-energy X-ray beam. By use of high-energy synchrotron X-rays, very sensitive measurements were achieved. It is estimated that Bragg diffraction peaks would be observed if the sample contained ∼0.1 volume percent or more of crystalline material. Previous techniques for making amorphous pharmaceutical compounds often result in products that contain crystalline materials (Nagapudi and Jona 2008).

The results of this work demonstrate that containerless methods enable the synthesis of amorphous pharmaceutical materials from low-molecular-weight compounds such as ibuprofen and carbamazepine that are difficult to make amorphous. Many of the low-molecular-weight materials form fragile liquids when they are melted. They are often very difficult to vitrify and usually form unstable glasses. Processing of supersaturated solutions or supercooled liquids provides routes to amorphous or glassy forms of materials. Glassy samples of carbamazepine have been produced by laser melting and quenching. Carbamazepine is a mood-stabilizing and anticonvulsant drug which has been classified as an organic molecule with very poor glass-forming ability (Nagapudi and Jona 2008). Work is in progress to investigate the effects of stabilizers on the glass-forming tendency and the stability of glassy and amorphous pharmaceutical products made from levitated liquids and solutions.

Structural evolution in high temperature liquids has been studied extensively by use of in-situ X-ray and neutron measurements of structure (Benmore et al. 2010; Drewitt et al. 2011). Making similar measurements at lower temperatures will help to develop a comprehensive understanding of the way in which molecular liquids transform into glasses. Recent work on molten oxides shows that the liquids can significantly restructure when they are supercooled (Benmore et al. 2010). In molten calcium silicates, the extent to which CaO_6 polyhedra edge-share increases when the liquid is supercooled (Benmore et al. 2010). A recent theoretical analysis suggests that structural changes are a general property of liquids when they are supercooled to a glass. These changes are particularly pronounced in fragile liquids for which super-Arrhenius viscosity changes with temperature are observed (Mallamace et al. 2010).

In-situ adjustment of sample chemistry can be used to control precipitation reactions and bulk chemistry. For example ammonia can be used to increase the pH of an acidic solution. Carbon dioxide or hydrogen chloride can reduce the pH of an alkaline solution. Chemical vapor deposition precursors could also be used to add components to a droplet. Understanding the nucleation mechanism is useful in, for example, improving the technology for bone replacement in which formation of hydroxyapatite is an important step (Hench and Wilson 1993). The use of in-situ pH changes to facilitate kosmotropic behavior has potential applications in salting out proteins from levitated drops of solutions. Acoustic levitation would enable non-contact processing to investigate the nucleation and growth of these types of material.

Acoustic levitation is a practical method for making amorphous pharmaceutical materials. The technique complements instrumented ball milling that has been a powerful tool in understanding the kinetics and thermodynamics of glass formation in a variety of pharmaceutical and organic materials (Willart et al. 2010). Combined with in-situ measurements of structure, acoustic levitation enables investigation of the evolution of structure during processing. This information provides insights into non-equilibrium reaction mechanisms. The techniques are useful for drug screening and production. Large-scale production using containerless methods could be implemented by using multiple automated levitators or with drop-tube techniques (Shahrokhi et al. 1990) optimized for this purpose.

Work is in progress to investigate the long-term stability of materials made amorphous by use of levitation methods. The on-gong work includes investigation of the time–temperature-transformation characteristics of supercooled liquids and studies of the effects of adding stabilizers to the compositions before they are processed.

Conclusions

Acoustic levitation enables investigation of metastable liquids under a variety of conditions. The experiments reported here demonstrate the ability to study:

1. supersaturated solutions;
2. supercooled liquids; and
3. the effects of in-situ changes of the pH of a solution.

Containerless conditions enable access to new forms of materials. Several pharmaceutical materials were made in amorphous forms by evaporation of solvent from saturated solutions or by supercooling molten drops. Containerless techniques are useful for synthesis of new forms of pharmaceuticals and investigation of evolution of the structure of metastable materials.

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