USING CONTAINERLESS METHODS TO DEVELOP AMORPHOUS PHARMACEUTICALS

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Abstract

Background

Many pipeline drugs have low solubility in their crystalline state and require compounding in special dosage forms to increase bioavailability for oral administration. The use of amorphous formulations increases solubility and uptake of active pharmaceutical ingredients. These forms are rapidly gaining commercial importance for both pre-clinical and clinical use.

Methods

Synthesis of amorphous drugs was performed using an acoustic levitation containerless processing method and spray drying. The structure of the products was investigated using *in-situ* high energy x-ray diffraction. Selected solvents for processing drugs were investigated using acoustic levitation. The stability of amorphous samples was measured using x-ray diffraction. Samples processed using both spray drying and containerless synthesis were compared.

Results

We review methods for making amorphous pharmaceuticals and present data on materials made by containerless processing and spray drying. It was shown that containerless processing using acoustic levitation can be used to make phase-pure forms of drugs that are known to be difficult to amorphize. The stability and structure of the materials was investigated in the context of developing and making clinically useful formulations.

Conclusions

Amorphous compounds are emerging as an important component of drug development and for the oral delivery of drugs with low solubility. Containerless techniques can be used to efficiently synthesize small quantities of pure amorphous forms that are potentially useful in pre-clinical trials and for use in the optimization of clinical products.

General significance

Developing new pharmaceutical products is an essential enterprise to improve patient outcomes. The development and application of amorphous pharmaceuticals to increase absorption is rapidly gaining importance and it provides opportunities for breakthrough research on new drugs. There is an urgent need to solve problems associated with making formulations that are both stable and that provide high bioavailability.

Keywords: Amorphous Pharmaceuticals, Acoustic Levitation, Containerless, Spray Drying.

Introduction and Background

Many pipeline drugs have low solubility in their crystalline state and require compounding in special dosage forms to be effective when they are administered orally [1,2]. The use of amorphous formulations increases bioavailability and they are rapidly gaining medical and commercial importance [1]. The purpose of developing and using amorphous forms is to increase the solubility and metabolization of the Active Pharmaceutical Ingredients (API) in a compounded drug dose. Drug compounds that are ingested but do not dissolve can lead to several problems. These problems include: (i) a need for larger doses in order to achieve the required assimilation of API, (ii) irritation of or damage to a patient's gastrointestinal tract by undissolved material, (iii) excretion of undissolved material that can contaminate waste water and/or enter the food chain, and (iv) the added cost of (often expensive) drug compounds that are excreted. The issue of low solubility can be particularly problematic in pre-clinical trials where very large doses (up to 100 times normal) of API may be used in order to establish a drug's toxicity [3].

By using a non-crystalline form of a compound, the energy required to break down the crystalline structure (roughly equivalent to the latent heat of fusion) is already "built into" the material. The decreased energetic barrier to dissolution enables faster and more effective assimilation. Law, *et al.* [4] investigated the relative solubility of crystalline and amorphous forms of Ritonavir, a protease inhibitor developed and manufactured by Abbott Laboratories and used in the treatment of HIV. Data from [4] is presented in Fig.1. In all the cases investigated, the blood plasma concentration of API peaks about 2 hours after ingestion of the drug dose. The magnitude of the peak concentration achieved by the amorphous dosages is 5-12 times that of the crystalline form.

Fig. 1. Blood plasma concentration of Ritonavir as a function of time after oral administration of crystalline and three different amorphous forms. Adapted from [4].

Hancock and Zograf [5] pointed out that, "The high internal energy and specific volume of the amorphous state relative to the crystalline state means that during processing or storage the amorphous state may spontaneously convert back to the crystalline state." This statement captures the essence of both the opportunity that amorphous pharmaceuticals provide and the potential problem of stabilizing them to achieve consistent performance over time. A drug that is compounded to deliver the required dose when it is amorphous is unlikely to do so if any significant crystallization occurs before it is administered. The possibility of crystallization during storage must be factored into the development and compounding of an amorphous drug. Stabilization of non-equilibrium forms requires kinetic inhibition of

crystallization to the more thermodynamically stable crystalline form. In general, kinetic stabilization of amorphous states occurs when transport processes slow down to a point where structural relaxation effectively stops [6]. For inorganic network glasses (such as silicates) that typically have high equilibrium melting points, stabilization at room temperature is easily achieved and structural relaxation effectively stops at the glass transition. For organic molecular glasses, stabilization is more challenging and small changes in the storage environment can strongly affect stability [7,8].

In this paper we emphasize novel synthesis methods and issues relating to the stabilization of amorphous forms. We recognize that some compounds are easily amorphized and may even be difficult to crystallize. For such materials synthesis of stable amorphous forms is clearly straightforward. The challenge is to develop amorphous forms of compounds that have a strong tendency to crystallize. In such materials, amorphization can be achieved by appropriate processing and/or the use of binder phases that form an amorphous dispersion [9]. Binders and an excipient can act in a similar way to a “network former” (*e.g.* silica) in an inorganic glass. The API molecules can be incorporated into the glass as network modifiers. In principle, the addition of a sufficient amount of binder will enable almost any compound to be made amorphous but with a correspondingly low concentration of API. The essential objective is to obtain stable amorphous forms that can deliver a high API dose with minimal addition of inert components.

Methods for Synthesizing Amorphous Drugs

Making amorphous forms requires bypassing the thermodynamic tendency for materials to nucleate and crystallize. In general, non-equilibrium amorphous or glassy products can be obtained by: (i) precipitation from solution, (ii) supercooling of melts, (iii) condensation of vapors, (iv) compression or milling of crystals, and (v) radiation disruption of crystals. In the context of making amorphous pharmaceuticals, the first four of these methods are used in various configurations [10-24]. Nagapudi and Jona [25] reviewed some of the widely used methods. Table I summarizes the major methods used to make amorphous drugs.

Table I. Methods for making amorphous drugs, adapted from ref. [25].

Method	Yield (%)	Scalable	Reference
Melt quenching	60-70	No	10,11
Ball milling	50-70	No	12
Cryogrinding	40-50	No	13,14
Desolvation	-	No	15
Lyophilization	75-85	Yes	16,17
Spray drying	40-75	Yes	18-20
Precipitation	75-85	Yes	21
Containerless processing	100		22-24

Each of the techniques identified is suited to specific types of compounds. Melt quenching can be used for materials that are thermally stable to a temperature slightly above their melting point. Melt extrusion is a scalable variant in which drug compounds are dispersed in a binder phase and extruded through a die. Lyophilization is effective for water soluble and hydrated compounds. Milling is commonly used to blend and size products prior to tablet production. Cryogrinding uses low temperature (typically liquid nitrogen) to stabilize non-

equilibrium forms of materials. Solution based processing employs volatile solvents that can sometimes be recycled in scaled up production. Very few methods are suitable for scaled up manufacture of amorphous products. Spray drying is one of the most promising methods for production due to its flexibility. It can be performed on a laboratory scale or used to produce multi-kilogram quantities of material. Spray drying can lead to high yields of amorphous products. Crystals are usually present in spray dried materials and we attribute this to contact with the walls of the process vessel, interactions between particles and nucleation induced by the ejection of material from the injection nozzle used to atomize the liquid.

Containerless Synthesis

Extrinsic heterogeneous nucleation normally prevents the supercooling or supersaturation phenomena that are important processing steps to make glassy and amorphous materials. The innovation in this work was to use containerless (non-contact) methods that completely avoid extrinsic heterogeneous nucleation and so enable many drugs to be made in amorphous forms. In addition, the use of containerless methods allows very high purity or “phase-pure” drugs to be made in many cases. The absence of binder phases provides useful information about the end member of the drug-binder binary phase diagram.

As indicated in Table I, the yield of amorphous material is substantially less than 100% for all of the methods except containerless processing. Containerless processing of pharmaceuticals was first reported by Leiterer, *et al* [26] who used acoustic levitation to investigate crystallization of aspirin from a solution in ethanol. Benmore and Weber used acoustic levitation to avoid extrinsic heterogeneous nucleation in supersaturated and supercooled liquids and obtained phase-pure amorphous products from a variety of pharmaceutical compounds [22]. We attribute the lower yields from the techniques listed in Table I to nucleation of crystals probably due to contact with process containers. In principle, all methods could be used to make 100 % amorphous product by adding sufficient binder to the drug material. We used compositions containing a high proportion of binder phases in order to compare samples made using spray drying and containerless processing as described later in this paper.

Acoustic levitation can be used to suspend and manipulate small drops and solid particles without contact in analytical applications [27,28]. Interference acoustic levitators were developed by Whymark [29], Rey, *et al.*, [30] and Trinh, *et al.*, [31]. The acoustic frequency is ultrasonic, typically 20-70 kHz where the wavelengths are 5-17 mm in air at room temperature. Simple interference acoustic levitators use a single transducer and an opposed reflector. A single transducer-reflector arrangement can provide stable levitation but it does not enable manipulation of the sample. Single-axis levitators that use two opposed active transducers can control sample position by electronically adjusting the relative acoustic phases. Phase control can be operated continuously or in controlled steps to provide a non-contact “production line” to synthesize and test formulations [32]. This approach is being developed using computer control of the levitator functions. A non-contact production line can enable partial automation of synthesis. If it is integrated with other instruments, *in-situ* characterization could be used to accelerate development of new materials for clinical trials.

In the present work a two-transducer acoustic levitator was integrated with a high energy x-ray beamline to enable *in-situ* diffraction measurements to be made. This capability allows the investigation of non-equilibrium behavior in solutions and low melting

materials. The results showed that a number of “difficult” glass formers could be synthesized in amorphous forms, in many cases as phase-pure compositions [22-24]. One configuration of the levitation system installed at a high energy beamline at the Advanced Photon Source (APS), Argonne National Laboratory is shown in Fig. 2. Additional configurations include integration of a 10 W carbon dioxide laser [23] to enable melting of samples and high speed video imaging to investigate drop deformation to derive thermophysical properties of liquids.

Fig. 2. Photograph of an acoustic levitator installed at a high energy beamline at the Advanced Photon Source. The two acoustic transducers are mounted vertically and seen near the center of the main image. X-rays are delivered along the center axis and intercept the levitated sample. Scattered x-rays are detected using a Perkin Elmer XRD 1621 amorphous silicon large area detector. An infrared imaging camera visible to the front left of picture was used to measure the sample temperature. A Cryostream was located close to the sample to allow cooling of the levitated drops. The inset image shows four levitated drops spaced at 7 mm intervals.

***In-situ* High Energy X-ray Structure Measurements**

High-energy x-ray diffraction measurements were made on levitated drops at various stages of the amorphization process. Experiments were performed at APS high energy beamlines using monochromatic beam energies of 100-115 keV [22-24]. Solutions of drugs in ethanol or acetone were investigated [22]. Phase-pure drugs were studied by melting levitated samples using a low power carbon dioxide laser [23,24]. The two-dimensional x-ray data collected were analyzed using the standard programs *FIT2D* [33] and *PDFGETX2* [34]. Results of prior work are summarized in the cited references.

Experiments were performed on saturated solutions of Atazanavir Sulfate-Polyvinyl Pyrrolidone (PVP) polymer mixtures. Atazanavir Sulfate is a protease inhibitor and it is among the most effective agents for treating HIV infections. It is currently sold under the trade name Reyataz®. PVP is a polymeric binder used in making drug products. It has structural groups that are strong acceptors for hydrogen bonds and it is useful as a glass former and stabilizer for amorphous formulations. Mixtures were made by dissolving the materials in stirred methanol held at 20°C in a temperature-controlled bath. The resulting solution was filtered to remove undissolved material and inserted into the acoustic levitator using a syringe. As the solvent evaporated, the droplet decreased in size as the solute supersaturated. Measurements were made on compositions containing 25, 50 and

75 mole% Atazanavir Sulfate balance PVP. Data measured for the three compositions presented in Fig. 3 show the three compositions of material after the solvent evaporation was complete.

The x-ray beam was smaller than the sample size and measurements were made on two regions of the sample by adjusting its position relative to the probe beam. The samples that contained 50 and 75 mole% PVP were amorphous in both regions that were probed. The sample that contained only 25 mole% PVP was amorphous in some regions and crystalline in others. This result is consistent with the composition containing only 25 mole% PVP being a marginal glass former.

Fig. 3. Data measured on samples formed by evaporating the methanol solvent from mixtures of Atazanavir Sulfate and PVP in different ratios.

Solvent Evaporation

Solution processing is frequently used in the formulation of pharmaceutical materials. An important step is the evaporation (and in large scale processes recycling) of the solvent to separate it from the product. Different solvents evaporate differently and can affect the amorphization of drug and drug-polymer mixtures. Acoustic levitation was used to investigate solvent evaporation in conditions similar to those found in spray drying. Data were obtained by injecting liquid into the levitator from a syringe and recording video images as the levitated drops evaporated. The acoustic forces were initially adjusted so that the levitated drop adopted an ellipsoidal shape. The major and minor axes (horizontal and vertical) of the ellipsoid were determined from the video images by calibrating the length scale with a precision reticle. The drop volume was then calculated from the relationship volume, $V = 4\pi/3 a.b.c$ where a, b and c are the orthogonal radii of the ellipsoid. Based on careful examination of the shape of stable, quiescent levitated drops, we assumed radial symmetry along the horizontal axes such that $a = b$. The calculated drop volumes were normalized to the initial volume of the drops. The horizontal dimension of the drops ranged from 1.2 to 3.1 mm when they were first levitated. Measured data for the normalized drop volume vs time for water, ethanol, methanol and acetone are presented in Fig. 4.

Fig. 4. Normalized drop volume for drops of different solvents levitated and held in still air. The lines connecting the points are to guide the eye.

The solvents were inserted into the levitator at a temperature of 20 °C. An experiment was also performed using acetone that was pre-cooled to a temperature of 5 °C prior to insertion. The use of highly volatile solvents such as dichloromethane is another possible way to cool levitated drops *in-situ* [35]. Tests show that the difference in measured evaporation rates between acetone introduced at 20 and 5 °C was insignificant. This finding suggests that the drop temperature rapidly equilibrates due to the interplay of: (i) thermal equilibration with the ambient gas temperature during and immediately after insertion, and (ii) the effects of “self-cooling” due to the latent heat of evaporation of the solvent. It would be possible to use temperature control to adjust the rate of solvent evaporation. However, as the present results suggest, it would be necessary to control the temperature of the volume of gas around the drop rather than simply to cool the solvent before insertion. The evaporation rate of dichloromethane was sufficiently large that the drop cooled very rapidly and formed a small spheroid or an irregular shaped piece of ice after 10-20 seconds. As a result of the rapid evaporation and icing, it was not possible to measure the time dependence of volume for dichloromethane.

The vapor pressures of water, ethanol, methanol and acetone at 20 °C are 0.4, 1.1, 2.2 and 4.1 kPa respectively [36]. Based on the relative slopes of the lines in Fig. 4, the measured evaporation rates for the faster evaporating solvents acetone and methanol are slightly less than the vapor pressure at 20 °C would suggest. We attribute these differences to: (i) self-cooling of the drops, decreasing the evaporation rate, (ii) uptake of water condensing onto the drop, increasing its volume, and (iii) the uptake of water reducing the activity of the solvent. The presence of water is further suggested by the observation that the size of drops formed from the fast evaporating solvents acetone and methanol initially decreases linearly with time then plateaus at a non-zero value. Condensation may be a significant effect when a solution of drug is evaporated since the water can be incorporated into the resulting product. Work on these types of solutions may require using a purged enclosure around the levitator to exclude water vapor and prevent condensation.

The drop evaporation measurements provide a qualitative measure of solvent behavior as it relates to spray drying processes. As the drop radius decreases its surface area:volume increases. This effect tends to increase the evaporation rate as a drop shrinks.

Comparison to Spray Drying

A 3:1 mixture of PVP and Atazanavir Sulfate was used to compare the structure of samples made by both levitation and spray drying. The mixture used contains a sufficiently large concentration of polymer that it can be made amorphous by both spray drying and containerless processing to completely avoid crystallization. It therefore provides a useful sample material with which to compare materials made by different routes since none of them should contain crystals. Normally, spray dried materials contain a substantial proportion of crystals [25] that would make it more difficult to make a direct comparison of the products. Samples with similar compositions were processed using a Buchi mini spray dryer and an acoustic levitator. The spray-dried particles were further dried in a vacuum oven.

One of the main differences between acoustic levitation and the spray drying process in pharmaceutical production is droplet size. The droplet size of samples prepared by levitation are typically ~ 0.5 - 1.0 mm in diameter, leaving particles sizes of ~ 300 - 500 microns after the solvent evaporates. In spray drying the particle sizes are typically in the range of 10 - 100 microns. The larger surface area:volume of small radius drops will increase the rate of solvent loss. The measured x-ray structure factors for 1:3 Atazanavir Sulfate:PVP are shown in Fig. 5.

Fig. 5. Comparison of x-ray structure factors measured for 1:3 Atazanavir Sulfate:PVP mixtures processed in methanol using containerless processing in the acoustic levitator and spray drying in a Buchi laboratory spray drier.

Apart from subtle differences in the low- Q region of the diffraction patterns, the measured structure factors are essentially the same, indicating that similar amorphous material is produced by both methods. Since any amorphous material may have a range of structures, the precise atomic or molecular arrangement is dependent on the thermal history or processing route used [25,26]. The changes in the low- Q region of the x-ray diffraction pattern reflect this and show differences in the first sharp diffraction peak and principal peaks which are attributed to differences in the intermediate range ordering of the system [27]. For molecular liquids, intermediate range order is usually associated with the packing arrangement of the molecules.

Measuring Surface Tension from Droplet Oscillation

For a given density material, the size of liquid drop that can be levitated is ultimately limited by its surface tension. The surface tension of a liquid also influences the way in which a droplet responds to external forces and affects how a droplet fragments if the

acoustic forces are increased sufficiently beyond the level required for levitation. In order to investigate induced oscillation of a drop, the acoustic amplitude was sinusoidally modulated by $\pm 10\%$ above and below the nominal value required for stable levitation. The effect of modulating the amplitude was to change the force on the drop mainly along the vertical axis. Increasing the force along the vertical axis tended to flatten the drop into an oblate sphere. The response of the drop shape to the changing forces was investigated by video imaging at a rate of 1000 frames per second. The drop shape changed from nearly spherical shape to an oblate sphere in phase with the force modulation.

The extremes of the shape change are illustrated in Fig. 6 that shows still images of a drop taken from the video record. The video images were analyzed to determine the width and height of the drop as a function of time. The cyclic change in drop width when it was excited at a frequency of 106 Hz is shown in Fig. 6. When the modulation frequency of the acoustic force was scanned over a range from about 80-120 Hz (at constant average acoustic force), the corresponding drop oscillation exhibited a maximum amplitude over a narrow frequency range. We attribute the maximum in the drop oscillation amplitude to excitation at its resonant frequency as first described by Rayleigh [36] and further investigated by Nelson [37]. Trinh [31] proposed using resonant excitation of acoustically levitated drops as a non-contact means to measure the surface tension of liquids. Trinh suggested that measurements could be made to an accuracy of 5% by using sufficiently precise spatial resolution imaging. Based on the feasibility experiments performed in this work, surface tension measurements could quite easily be implemented by using higher spatial resolution imaging of the levitated drops.

Fig. 6. Left: Images of the drop in at the extremes of motion. Right: Plot showing the drop width (arb units) vs. time (taken from the video record) for a drop being excited at a frequency of 106 Hz. The points are the data, the line is a sine function fitted to the data.

Stability of Amorphous Forms

Many pharmaceutical compounds form fragile liquids that are difficult to vitrify [39,40]. In fragile liquids, transport processes typically continue at relatively high rates into the deeply supercooled temperature range. The continued structural relaxation even close to the glass transition increases the possibility of residual crystals in the product and these can seed further crystal growth during storage. The short term stability of marginally stable amorphous forms may be sufficient for use in pre-clinical research [39]. However, changes in the amorphous:crystalline content over time can affect uptake of API limiting their use for clinical applications.

A simple concept for stabilizing amorphous phases is to make them 100% amorphous and so avoid introducing any seed crystals into the initial product. Containerless processing is a way to achieve phase-pure amorphous forms in many cases. Phase-pure amorphous products were made by containerless cooling of supercooled melts [23]. The crystalline content of these materials was measured over time after they were made. The data presented in Fig. 7 shows results of measurements of crystal content in Miconazole Nitrate and Carbamazepine. The percentage of crystals was determined by comparing the intensity of the measured Bragg peaks and diffuse scattering from the sample with a linear combination of the fully amorphous X-ray spectrum and a fully crystalline powder average of the starting material [23].

Fig. 7. Plots depicting time dependence of the degree of crystallinity in initially amorphous samples formed using containerless processing in an acoustic levitator. The different symbols represent single samples of the compound, typically three and six for each drug, where 100% represents the crystalline starting material and 0% represents a fully amorphous material exhibiting no Bragg peak scattering. Adapted from [23].

It has proved difficult to accurately predict the stability of amorphous materials over time for the types of molecular glass investigated in this work. For example in the cases

presented in Fig. 7, the glass transition temperatures of Miconazole Nitrate and Carbamazepine are 1° and 61 °C respectively [39]. The samples were stored at a temperature of 2 °C. In spite of this, the Carbamazepine crystallized quite rapidly whereas the Miconazole Nitrate did not. This result indicates that in amorphous Carbamazepine, structural relaxation occurs even at about 60 degrees below the glass transition temperature.

It may be tempting to try and classify crystallization tendency based on the form of the individual drug molecules. However, this approach may prove to be unsatisfactory. Two widely studied materials are Felodipine and Nifedipine [8,42]. Even though these materials have quite similar molecular structures (see illustrations in Fig. 8) the amorphous forms have very different stabilities.

Fig. 8. Diagrams illustrating the molecular structures of Nifedipine (left) and Felodipine (right). The amorphous form of Felodipine is stable whereas Nifedipine crystallizes readily even at temperatures below its glass transition of ~42 °C [8].

Felodipine can be made into a glass that can be stored for extended periods at room temperature without crystallization. Amorphous Nifedipine crystallizes in a short period of time at room temperature. While these materials have been investigated, the mechanism of crystallization considerably below the glass transition is not well understood. Marsac, *et al.* [8] discuss the observed differences in terms of the free energy of crystallization but do not arrive at any conclusive structural basis for the observed differences. Miyazaki, *et al.* [42] also point out that crystallization in different forms of Nifedipine is related to differences in the free energy of crystallization but do not have a clear predictive model of behavior of the glasses. Bhattacharya and Suryanarayanan [43] discuss the role of β or Johari–Goldstein relaxation in glassy pharmaceuticals at temperatures below the glass transition. These relaxations may result in local formation of nuclei that subsequently grow throughout the glass. The crystallization mechanisms in amorphous pharmaceuticals is not well understood and it is not yet possible to reliably predict the behavior of materials. There are interesting opportunities for further work to understand this special class of glassy materials. Factors such as structural resonances can influence the energetics of relaxation in ways that do not occur in inorganic network glass formers. Containerless processing provide a useful tool to synthesize phase-pure samples that can be used to benchmark behavior of the end member of binary drug-binder phases.

Conclusions and Outlook

The work reported and cited here leads to several conclusions as follows:

1. Synthesis of amorphous forms of pharmaceutical materials is an increasingly important research area due to the low solubility of many crystalline pipeline drugs.
2. Spray drying is the production method that is emerging as the preferred way to scale up production of amorphous pharmaceutical products.
3. Containerless methods completely eliminate extrinsic heterogeneous nucleation and they can be used to make samples of phase-pure amorphous drugs even from reluctant glass formers.
4. Acoustic levitation was shown to be suitable for containerless processing of supersaturated solutions and supercooled melts formed from drug and drug-binder samples.
5. *In-situ* structure measurements provide a useful tool to follow the process of amorphization.
6. Samples made using containerless processing and spray drying have similar structures. This finding suggests that acoustic levitation can be used in development and characterization of materials that can be scaled up using spray drying.
7. Predicting the stability of amorphous forms proved to be difficult. Empirical measurements of crystalline content as a function of time provides essential data.

There are important research opportunities to extend both the synthesis and stabilization of amorphous forms of pharmaceutical materials. From the present and prior work, it is apparent that prediction of the stability of an amorphous form is difficult and currently only empirical measurements can be relied upon in most cases. Combining acoustic levitation with *in-situ* probes such as x-ray and potentially neutron techniques extend the ability to investigate the role of structural evolution in the process of amorphization and relaxation. Work to develop a better understanding of the mechanisms of relaxation, the role of residual seed crystals and the processing route are needed in the further development of amorphous drug formulations.

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