

SUPERCRITICAL ANTISOLVENT CRYSTALLIZATION OF ADIPIC ACID USING AN HABIT MODIFIER

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In this study, the crystal morphology of adipic acid mediated by the action of urea as additive has been investigated. The process was performed using acetone and carbon dioxide as solvent and antisolvent, respectively. The effect of urea concentration in the liquid solution and of precipitation pressure on the crystals habit was investigated; the products were characterized by scanning electron microscopy (SEM), X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and infrared spectrometry (FT-IR). Urea was found to be very effective in modifying the crystal habit of adipic acid from needle-like shape with a length of several hundreds of microns to prismatic shape of micrometric dimensions. Operating at 40 °C, 12 MPa and an urea/adipic acid mass ratio of 12.5% prismatic crystals with a mean size of about 7.5 μm and a very narrow crystal size distribution were obtained. Upon crystallization, urea is partially extracted by CO₂ in the final washing step of the process, and the remaining part is entrapped within adipic acid crystals forming a solid mixture. The modification induced by urea on the crystal habit and size of adipic acid can be attributed to a preferential adsorption mechanism of urea to the fastest growing crystal face of needle crystals, that in the case of adipic acid is the face in which the higher concentration of carboxylic groups is present.

INTRODUCTION

The manipulation of polymorphism, morphology and size of crystals of micro or nanometric dimensions is a relevant industrial challenge due to their strong influence on materials properties. Crystal morphology, or habit, can influence many downstream relevant properties, such as filterability, flowability, compactability and dissolution time. The proper crystal habit and size are essential for manufacturing processes such as powder mixing and filling. For this reason, there is an increasing interest in the speciality chemicals industries to develop technologies and methods that can produce crystals at micro and nanoscale levels with controlled properties such as crystal size (CS), polymorphism and habit. Crystallization is most commonly employed as the final step in the preparation of products with desirable crystal form and dimension. However, some products very often crystallize in acicular or needle shape, thus producing undesirable flow characteristics, low bulk density, caking, and difficulties in packaging and handling of the material. To avoid these problems, milling or crushing are often employed to eliminate the undesired shape of the particles and to reduce CS. However, milling may generate thermal degradation, contamination, differences among different product batches and increase the amorphous content that reduce the quality of the product.

Alternative efficient processes that use supercritical fluids (SCFs) as processing medium for the production of micro and nano-sized particles have emerged. Among them, semiconscious supercritical antisolvent (SAS) precipitation has emerged and successfully applied to many organic and inorganic substances. The mean particle size that can be obtained by SAS ranges from about 0.05 μm to tens of microns and different morphologies can be produced depending on the processed material. It is a very rapid process if compared to the traditional liquid-antisolvent crystallization and for this reason, amorphous spherical particles are a common habit and they are frequently the scope of the process. However, some substances can form crystals even at high pressure and large CO₂ concentration with

respect to the liquid solvent. In these cases, unfortunately, the size of the product is hard to control and large CS and wide distributions (CSDs) are usually obtained.

A general processing strategy that can be used to modify CS and crystal habit is the use of habit modifiers to selectively change crystal growth kinetic during crystallization. This method is advantageous because crystal habit can be modified without onerous post-processing operations. It is well known that nucleation, growth, polymorphism and habit of crystals can be significantly altered by the presence of low concentrations of additives purposely added to alter the crystallization process. Additives can reduce crystal growth rate and alter morphology by binding to crystal face and interfering with the propagation steps¹. In some cases, the additives substitute in the crystal lattice and disrupt the binding sequence^{2, 3}. In either cases, however, if the additive selectively interacts with a particular crystal face it will slow only the growth rate of that face and alter the morphology of the crystal. Until now, the use of additives as habit modifiers during supercritical fluid crystallization has been studied in a very reduced number of works⁴⁻⁶.

In this work adipic acid has been selected as model compound due to its capability to form hydrogen bonds with urea. Urea is an end product of human protein metabolism and possesses several features which make it an attractive additive: it is non-toxic, biodegradable, non-smelling and can be generally considered to be safe for human body. Urea was selected as a crystal modifier for its molecular structure, selective interactions with adipic acid molecules and solubility in acetone, that was used as solvent in this work.

The scope of this work has been the SAS precipitation of adipic acid from acetone in the presence of urea used as an additive to control polymorphism, crystal habit and dimensions of crystals.

The effect of the main process parameters on powder properties were investigated and crystals were extensively analyzed using various techniques, as SEM, DSC, FT-IR spectroscopy and XRPD.

MATERIALS AND METHODS

Materials and Analytical Methods

Adipic acid [(CH₂)₄-(COOH)₂] and urea [CO(NH₂)₂] purity 99.5% were purchased from Sigma-Aldrich (Italy). Acetone (purity 99.8%) was purchased from Carlo Erba Reagenti (Italy). CO₂ (purity 98%) was purchased from SON (Italy). All products were used as received. The solubility of adipic acid in acetone was measured and resulted at 20 °C about 1.3 wt%. Untreated adipic acid was composed of boulder like crystals with irregular shapes and a large CSD, ranged between 20 and 300 μm.

Scanning Electron Microscopy (SEM). A LEO 420 (USA) microscope was used for the analysis. Powders were dispersed on a carbon tab previously stuck to an aluminium stub. Samples were coated with gold-palladium (layer thickness 250Å) using a sputter coater (Agar Scientific, UK). Several SEM images from different parts of the precipitation vessel were taken for each run to verify the powder uniformity. Particle size and particle size distribution (PS, PSD) were evaluated from SEM images using the Sigma Scan Pro 5 Software (Systat Software Inc., Usa). Depending on the sample, about 200-400 crystals were considered in each size distribution calculation. Histograms representing the crystal size distribution were best fitted using Microcal Origin 7.0 Software (Microcal Software Inc., USA).

Differential Scanning Calorimetry (DSC). Calorimetric analysis has been performed using a DSC Mettler TC11 (USA). Temperature and enthalpy of fusion were calibrated with pure indium standard (melting point 156.6 °C). Powder samples (5±0.5 mg) were accurately weighed, crimped in an aluminium pan and heated from 25 °C to 170 °C at 10 °C/min under a nitrogen purge. Melting points were calculated using the software provided with the instrument.

Experimental Apparatus. The SAS apparatus consisted of a modified HPLC pump equipped with a pulse dampener used to feed the liquid solution, and a diaphragm high-pressure pump used to deliver carbon dioxide. A windowed vessel of 0.375 dm³ with two quartz windows put along the longitudinal section was used as the precipitation chamber. It allowed to visualize the kind and number of fluid phases of the mixture formed during precipitation and to follow the macroscopic evolution of the process from the liquid jet breakup to the deposition of precipitated particles. A video camera placed in front of one window allowed to record the experiments.

The liquid mixture was sprayed in the precipitator through a thin wall stainless steel nozzle (60 μm in diameter, 800 μm in length) and SC- CO_2 was pumped through another inlet port located on the top of the chamber. CO_2 was heated to the process temperature before entering the precipitator. A stainless steel sintered metal disk was put at the bottom of the chamber to collect the solid product, allowing the CO_2 -organic solvent solution to pass through. When antisolvent steady flow was established and the desired pressure was reached, pure liquid solvent was sent through the nozzle to the precipitation chamber at a flow rate of 1 mL/min in co-current mode with supercritical CO_2 , which flow rate was regulated to obtain a CO_2 mole fraction of 0.98 inside the precipitator. Then, the flow of the liquid solvent was stopped and liquid solution was delivered through the nozzle at 1 mL/min flow rate. The experiment ended when the delivery of the liquid solution to the chamber was interrupted. However, supercritical CO_2 continued to flow for further 60 min to wash out the residual content of acetone contained in the chamber. Precipitation experiments were repeated twice.

RESULTS

Effect of process conditions on the crystal habit of adipic acid.

The SAS-precipitation of pure adipic acid from 1.26 wt% acetone solutions was first performed at 40 $^\circ\text{C}$ and 80, 120 and 150 bar. **Figure 1** shows a representative SEM micrograph of adipic acid crystallized at 120 bar. As shown in the figure, at these conditions adipic acid crystallizes as long needles. The crystal population is unimodal, crystal dimensions are comprised between 100 and 750 μm with a mode of about 250 μm (the main axis of needles has been chosen as characteristic length). The widths of the crystals were approximately an order of magnitude smaller than the lengths. Experiments at 80 and 150 bar lead to the same needle-like habit with a mode of 225 and 220 μm , respectively. Operating SAS precipitation at 40 $^\circ\text{C}$ and pressure in the range 100-150 bar, nanoparticles formation has been frequently observed; but the formation of large crystals with a limited possibility of controlling their size, has also been reported by several authors for some other compounds^{19,20}. A possible explanation of the formation of large crystals of adipic acid at this conditions of temperature and pressure was found observing the precipitation process in a quartz windowed vessel: a clear solution filled completely the vessel and no phase transitions were observed during the whole experiment. After about five minutes from the starting of the injection, the formation of large adipic acid crystals was observed mainly on the precipitator walls. Due to the partial solubility of adipic acid in the mixture SC- CO_2 – acetone, adipic acid is partly solubilized in the fluid phase until supersaturation occurs and thus adipic acid precipitates from a ternary solution acetone- CO_2 -adipic acid, different from the starting binary supercritical mixture acetone- CO_2 . Thus, liquid-like nucleation and growth process is obtained that is mainly controlled by the residence time of the solute in the precipitator and is, of course, different from the one that produces nanoparticles formation from supercritical solutions.

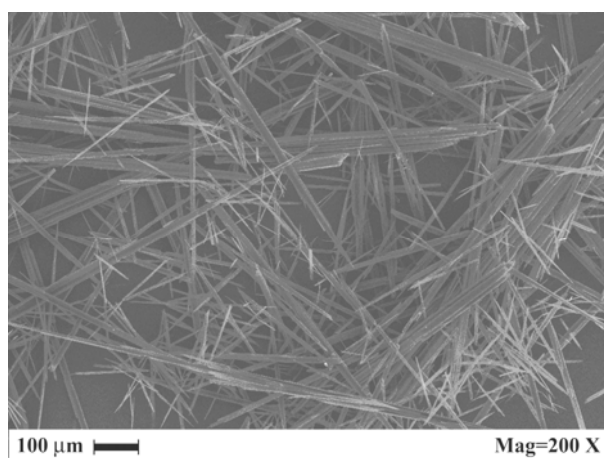


Figure 1. SEM image of adipic acid crystals obtained by SAS precipitation at 40 $^\circ\text{C}$, 120 bar and 1.26 wt% of adipic acid in acetone.

Effect of the presence of urea. Needle-like habit of adipic acid is not unusual and it was also observed when cooling crystallization was carried out in the presence of a proper anionic surfactant⁷. Surfactant molecules are able to be absorbed more strongly into the crystal faces parallel to axis of the adipic acid molecules, causing retardation of their growth rates. This behaviour is related to the surfactant concentration and, at higher concentration, the formation of long needles was observed⁷. Thus, the decrease in the growth rate of individual faces due to the effect of the additive is probably solely responsible for the habit modifications of adipic acid crystals. Thus, a possible way to control adipic acid crystal size and to selectively modify crystal habit is to add a crystallization modifier; i.e., an additive with the scope of growth inhibitor of the crystallization process. Therefore, in this work urea has been chosen because of its capability to form hydrogen bonding with carboxylic groups of adipic acid. Adipic acid was SAS-precipitated from acetone at 40 °C and 120 bar and at different values of urea concentration, namely 0.08, 0.16, 0.24 and 0.32 wt%. **Figure 2a** shows the SEM micrograph of the crystals generated at the lowest urea concentration; i.e., 0.08 wt%, where the crystal shape is acicular with sizes in the range 20-40 µm. The dimensions of crystals is about an order of magnitude smaller than that of crystals obtained at the same operating conditions without urea (**Figure 1**). When the urea concentration was increased to 0.16 wt% (corresponding to an urea/adipic acid mass ratio of 12.5%), prismatic crystals were obtained with a smaller crystal size (**Figure 2b**). The crystal population was unimodal, crystal sizes are ranged between 2.5 and 30 µm with a mode of about 7.5 µm. The width and depth of prisms were of the same order of magnitude than the main diagonal. Thus, an effective change of crystal habit and size was obtained. When the urea concentration was increased to 0.24 wt%, two different crystal populations were obtained: one with a prismatic shape and dimensions of about 20 µm, and one with an acicular shape and dimensions of several microns. Thus, in this case urea is only partially able to block the crystal growth. Finally, at the highest level of urea concentration (0.32 wt%), the crystal population is composed only by needles with a length from several microns up to 1 mm. Therefore, it is evident that the concentration of urea in the adipic acid solution plays a definite role in the precipitation mechanism. A concentration of 0.16 wt% seems an optimum value below and above which the modification effect is largely reduced. This behaviour is not new and unexpected, since some studies report growth enhancement occurring at low impurity levels followed by a reversal at higher levels when the interactions between additives molecules become dominant with respect to the interaction between additive and solute molecules⁸. Similar results were also observed in a previous work concerning the SAS-precipitation of sulphatazole in the presence of urea⁶.

The DSC thermograms of pure products, as expected, showed a single endothermic peak corresponding to the melting point of adipic acid at 151 °C and of urea at 134 °C. SAS-processed adipic acid showed the same melting temperature of the pure product. Also, sample obtained with urea at 0.08wt % had only one peak at 151 °C, as the pure product. When adipic acid samples processed in the presence of urea at 0.16 and 0.32 wt% were analyzed, two thermal events were observed: an endothermic peak at low temperature (110 °C), and a second endothermic curve, which is not isothermal, and peaks at higher temperature. This behaviour is typical of eutectic solid mixtures, where the first peak corresponds to the eutectic melting and the second peak corresponds to solid-liquid transition which temperature is function of the composition. When the concentration of urea was increased from 0.16 to 0.32 wt%, the eutectic peak area increased and the solid-liquid transition peak area decreased: the sample composition approaches the eutectic composition at which only the first peak should be present. This behaviour indicates that the SAS-precipitated samples contain a residual content of urea which is proportional to the initial concentration of urea in the solution. These findings were confirmed by a comparison with the thermal behaviour of urea:adipic acid physical mixtures. Precipitation carried out at higher urea concentration (i.e. 0.16 and 0.32 wt%) leads to mixtures with a composition minor to the eutectic. A comparison between the DSC curves of SAS-precipitated sample at 0.16 wt% and the physical mixture at the same concentration, shows that the eutectic peak area of the physical mixture is slightly higher than that of the precipitated sample. This fact indicates that, during precipitation, part of urea is extracted by CO₂. The formation of a solid

mixture characterized by eutectic upon SAS precipitation, supports the hypothesis that urea acts by a selective adsorption mechanism and it is not incorporated in the crystal structure. The effect of urea is likely due to the formation of hydrogen bonds between urea and adipic acid. The mechanism responsible for the habit modification can be a selective interaction of urea on faces normal to the axis of the adipic acid molecules, promoted by hydrogen bonds, which reduces the growth of these faces with respect to the faces parallel to the molecules axis, producing a prismatic habit with comparable dimensions of all edges.

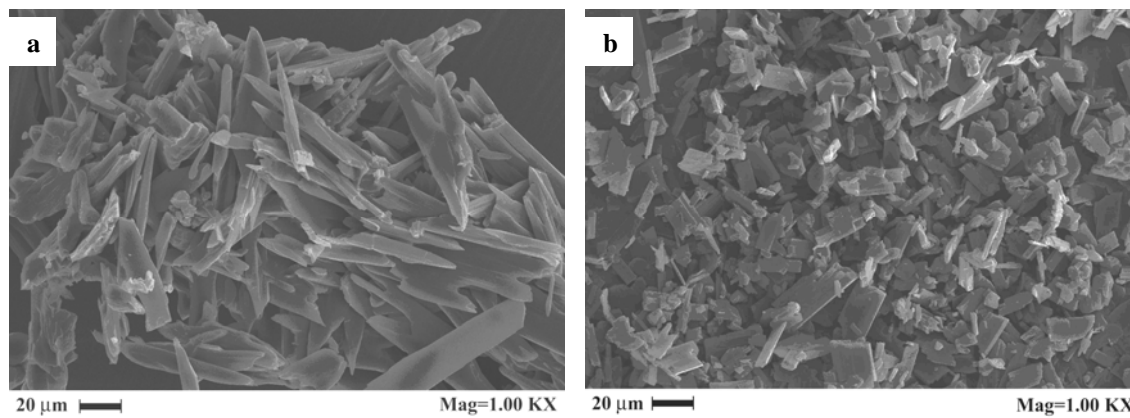


Figure 2. SEM images of adipic acid produced during SAS at 40 °C, 120 bar in the presence of urea at a) 0.08 wt %, b) 0.16 wt%.

Effect of the pressure in the presence of urea.

The effect of pressure on the precipitation of adipic acid in the presence of urea was also investigated. Experiments were carried on at 40 °C and 80, 90 and 120 bar at a fixed concentration of urea of 0.16 wt%. Precipitation carried out at 120 bar resulted in the formation of prismatic crystals of 7.5 µm mean size, as previously described (**Figure 2b**). As pressure is isothermally reduced to 80 bar the resulting crystal habit changed significantly. This can be readily seen by comparing SEM images reported in **Figure 1** to that reported in **Figure 3**. Particle morphology is completely different in shape and size from that obtained at 120 bar. Spherical particles with a uniform morphology and with a mode of about 4 µm were obtained. Spherical microparticles are a morphology that has been frequently observed during SAS experiments with various materials⁶. It is due to the jet break-up of the liquid solution and on the subsequent drying of the droplets formed upon atomization. This mechanism develops when temperature and pressure conditions lead to the formation of a vapour phase which is below the mixture critical point. Liquid droplets can form at the nozzle tip and, sustained by surface tension, their life-time is long enough to allow the precipitation of the solute within each droplet. In the case of adipic acid, the surface of microparticles is composed of very small crystals less than 1 µm in length. This fact can be explained considering that two mechanism in series are responsible of the formation of the particles: the first leads to the formation of spherical particles, and the second leads to the formation of crystals on the particle surface. The effect of urea superimposes to this complex mechanism. It is likely that urea acts as growth inhibitor of adipic acid during the “droplet confined” crystallization, producing small prismatic crystals that are visible on the surface of the expanded particles. Operating the precipitation at the same operating conditions without urea, long needles are formed because of the lack of the growth inhibition effect played by urea. Precipitation carried out at 90 bar resulted in the formation of both crystals with near prismatic shape and microparticles, probably because these operating conditions represent a transition between the two observed mechanisms.

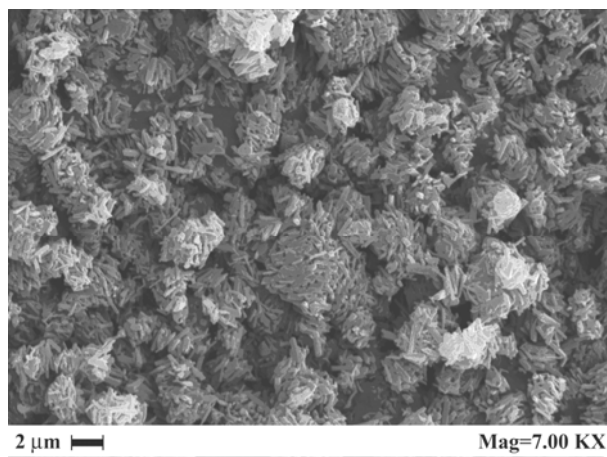


Figure 3. SEM images of adipic acid produced by SAS at 40 °C, 80 bar, in the presence of urea at 0.16 wt%:

CONCLUSION

The supercritical antisolvent crystallization of adipic acid from acetone using CO₂ as antisolvent and urea as habit modifier has been studied. The use of urea allows for a close control of crystal size and habit of adipic acid. Indeed, adipic acid crystal habit was modified from needle-like to prismatic with the addition of urea at 0.16 wt % in solution. The size of the crystals was reduced from several tens of microns to 7.5 μm. However, the effect of urea largely depends on its concentration with respect to adipic acid. 0.16 wt % of urea seems an optimum value below and above which the modification effect is largely reduced. Upon crystallization, urea is partially extracted by CO₂ in the final washing step of the process, and the remaining part remain is with adipic acid forming a solid mixture characterized by an eutectic. After precipitation, when crystal were washed with water, in which urea is largely soluble, it was observed that urea is completely extracted and adipic acid crystals were unchanged. Thus, it can be concluded that urea is not incorporated into the parent crystal structure. The modification induced by urea on the crystal habit and size of adipic acid can be attributed to a preferential adsorption mechanism of urea to the fastest growing crystal face of needle crystals, that in the case of adipic acid is the face in which the higher concentration of carboxylic groups is present. The obtained experimental results motivate further work and provide directions for future investigations about the potential of the use of habit modifiers in the supercritical antisolvent precipitation. The authors believe that coupling the well-known tunability of SCF based processed with the use of “tailor made” additives can greatly enhance the control of crystal habit and polymorphism of a large variety of products.

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