DELOS[â] PROCESS: CRYSTALLIZATION OF PURE POLYMORPHIC PHASES FROM CO$_2$-EXPANDED SOLUTIONS.

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The *DELOS*[®] process is a crystallization method for the straightforward production of nano and micron sized particles of organic compounds with a narrow size distribution. The driving force of this crystallization method is the high, rapid and extremely homogeneous temperature decrease experimented by a CO$_2$-expanded solution of the compound to crystallize when it is depressurized to atmospheric pressure. In the present work we show the influence of the *DELOS*[®] crystallization conditions over the polymorphic nature and purity of crystalline solids produced.

INTRODUCTION

The *DELOS*[®] crystallisation technique [1,2] is an efficient process, which uses a compressed fluid (e.g. CO$_2$), for the straightforward production of nano- or micron-sized crystalline particles. As in the *GAS* processes [3,4], the *DELOS*[®] technique is a crystallisation procedure performed using CO$_2$-expanded solutions. In the *DELOS*[®] process, however, the precipitation is caused by the high and greatly homogeneous temperature decrease ($\boldsymbol{D}T = T_F - T_W$) experienced by the CO$_2$-expanded solution when it is depressurised (see Figure 1). This temperature decrease is produced by the evaporation of the CO$_2$ from the expanded solution during the depressurization step. The higher is the CO$_2$ content of the solution the higher is the heat required for its vaporization, and consequently a higher temperature decrease is produced.
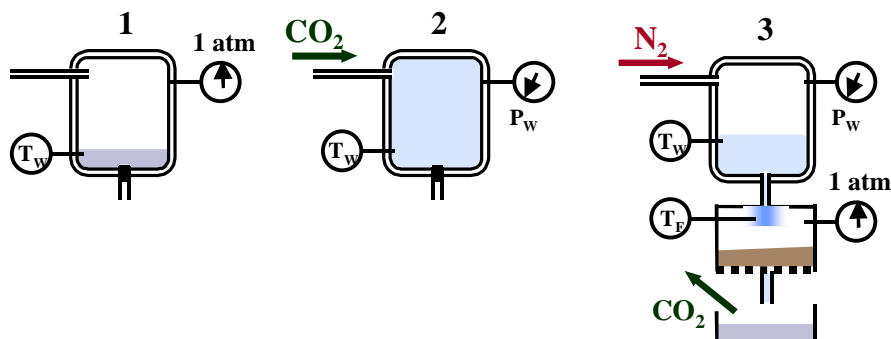
Figure 1. Different steps of a DELOS process: (1) A liquid solution of the compound to be crystallised is added to the autoclave. (2) Addition of CO$_2$ that produces a new expanded liquid solution, which fills all the autoclave volume at a given pressure, P_W, temperature, T_W, and molar fraction of CO$_2$,

X_W. (3) The solution is depressurised through a valve leading to the precipitation of monodispersed nano- or micron-sized particles.

Stearic acid, like other lipids and related long-chain compounds, may crystallise in different polymorphic forms depending on the conditions in which the crystallisation is performed. Up to now, there are described five polymorphic phases of stearic acid: two triclinic forms A_2 and A_3, belonging to what is called A-form, and three monoclinic forms called B, C and E having an orthorhombic subcell. Two of these forms, B and E, show the phenomena called polytypism, corresponding to a higher order structural difference caused by a different stacking sequence of the layers. In both B and E forms there are two polytypes: a single-layered structure with monoclinic space symmetry and a double-layered structure with orthorhombic space symmetry.

In this work we have used stearic acid as a probe molecule for studying the influence of the temperature decrease magnitude experimented during a $DELOS^{®}$ process on the polymorphic nature and purity of the crystalline solids produced.

MATERIALS AND METHODS

Stearic acid (purity 99%) was purchased from SIGMA-ALDRICH (Steinheim, Germany), ethyl acetate (purity 99%) from SDS (Peypin, France) and CO_2 (purity 99.9%) was supplied by Carburos Metálicos S.A. (Barcelona, Spain).

The crystallization of stearic acid through a $DELOS^{â}$ process was performed using ethyl acetate as conventional solvent and CO_2 as compressed fluid. The crystallization experiments have been performed using the same equipment described in previous works [1], and the operational procedure and experimental conditions used were as follows. A known volume of a solution of stearic acid in ethyl acetate, with a known initial supersaturation ratio, b_{R} was loaded in a high-pressure vessel. In all experiments the temperature (T_W) was kept constant at 298K. The initial solution was then pressurised up to a given pressure, which we call the working pressure (P_W), by the addition of a given amount of CO_2, X_W. After leaving the system under the same conditions for 30-60 minutes, in order to achieve a complete homogenization and its thermal equilibration, the solution was depressurized over a non-return valve from P_W to atmospheric pressure. As the solution depressurization starts, the temperature monitored after the depressurization valve decreases suddenly until reaching a constant value. This temperature value is taken as T_F. The precipitate produced through a $DELOS^{Ò}$ process, during the depressurization, was collected at atmospheric pressure on a filter placed after the depressurization valve. After the filtration, the cleaning of the precipitate was carried out with pure CO_2 at 3MPa and 293K during 60min.

RESULTS AND DISCUSSION

Several $DELOS^{®}$ crystallization experiments of stearic acid from "CO_2-expanded ethyl acetate", at 10MPa and 298K, were carried out with different values of CO_2 content. The polymorphic purity and nature of the crystals obtained were studied by FT-IR spectroscopy, powder X-ray diffraction (PXRD) and scanning electron microscopy (SEM), and compared to the polymorphic nature of the raw material. The structural changes between the different polymorphs of stearic acid are so small that their identification requires the combination of the different characterization techniques.

In Figures 2 and 3 are shown, respectively, the FT-IR spectra and PXR diffractograms of the unprocessed stearic acid polymorph A, and those of crystalline solids obtained in different $DELOS^{\hat{a}}$ experiments.
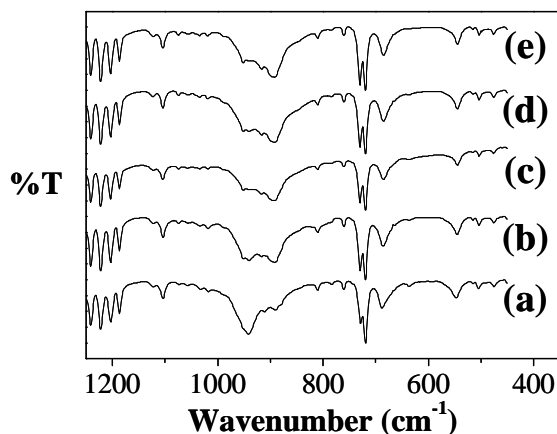
Fig. 2: IR spectra of: (a) unprocessed stearic acid A-form; $DELOS^{\hat{a}}$ processed stearic acid at: (b) X_W=0.3, DT=-20°C; (c) X_W=0.5, DT=-38°C; (d) X_W=0.7, DT=-68°C; (e) X_W=0.8, DT=-80°C.
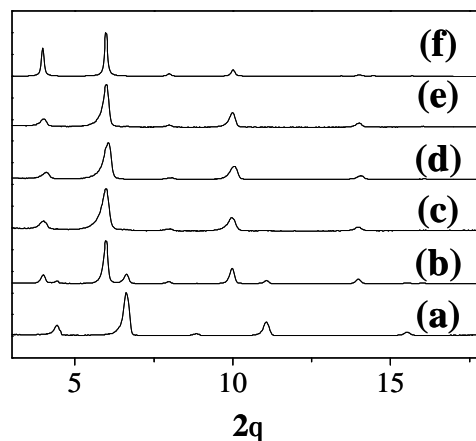
Fig. 3: PXR diffractograms of: (a) unprocessed stearic acid A-form; $DELOS^{\hat{a}}$ processed stearic acid at (b) X_W=0.3, DT=-20°C; (c) X_W=0.5, DT=-38°C; (d) X_W=0.7, DT=-68°C; (e) X_W=0.8, DT=-80°C.

PXR simulated diffractogram [5] obtained either from the orthorhombic polytype crystal structure of E-form or B-form (f).

The IR spectra of the unprocessed stearic acid A-form shows a strong band at 941cm^{-1}, which corresponds to the OH bending vibration band of the carboxyl group (δ_{OH}) [6]. However, in the IR spectra of the $DELOS^{\hat{a}}$ processed stearic acid at X_W=0.8 (profile **e** of Figure 2) this band appears shifted at 892cm^{-1}. The position of the δ_{OH} band and the thin plate morphology observed in the SEM images, reduces the possible polymorphic forms for the $DELOS^{\hat{a}}$ processed material to the B and E-forms. From the PXR diffractogram (see profile **e** of Figure 3), it is inferred that the crystalline stearic acid produced from "CO$_2$-expanded ethyl acetate" at X_W=0.8 has an orthorhombic polytype crystalline structure of either polymorph B or E forms. The distinction between these two orthorhombic forms comes out from the IR spectrum, since the OCO in-plane deformation band appears at 648cm^{-1} for the B-form while it apperas at 688cm^{-1} for the E-form [7]. Thus, in the IR spectra of the $DELOS^{\hat{a}}$ processed material (profile **e** of Figure 2) this weak band appears at 685cm^{-1}, which allow to assign definitively an orthorhombic polytype E-form crystalline structure to the processed stearic acid.

The FT-IR spectra and the PXR diffractograms of the different crystalline stearic acid solids obtained by $DELOS^{\hat{a}}$ crystallization at different values of X_W are shown, respectively, in Figures 2 and 3 (profiles **b** to **e**). As it can be observed, when the magnitude of DT is higher or equal to 38°C the crystalline solids produced show a pure orthorhombic polytype E-form (profiles **c**, **d**, and **e**). However, for values of DT lower than 38°C, for which lower solution maximum supersaturation levels are attained, although the orthorhombic E-form is the most

favoured form, FT-IR and PXRD indicate small amounts of A-form (profile **b** of Figures 2 and 3).

From these results it can be inferred that the orthorhombic E-form of stearic acid is favoured when using kinetically controlled crystallization procedures like the *DELOS*$^{\hat{a}}$ process, in which high supersaturation levels are rapidly and homogeneously achieved during the depressurization of the "CO_2-expanded ethyl acetate" solution.

CONCLUSION

In the present work it is shown that the DELOS$^{®}$ process is able to produce pure polymorphic phases, which are kinetically favoured and are difficult to obtain by other thermodynamically-controlled crystallization methods.

ACKNOWLEGDMENTS

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