Spherical Crystallization: Modeling of the Emulsion Solvent Diffusion Technique

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Abstract

Kawashima developed the spherical crystallization technique to produce shaped and sized particles with improved properties. He presented two methods: Spherical Agglomeration (SA) and Emulsion Solvent Diffusion (ESD). It was established that ESD proceeds from a spontaneous emulsion of the drug solution into a non-solvent liquid, whereas the solvent and the non-solvent are miscible.

We investigated the general pharmaceutical case of a drug substance (DS) which is highly soluble in acetone (S) and moderately soluble in water (NS). The phase diagram DS/S/NS confirms that a concentrated DS/S solution poured into an NS will generate a biphasic liquid/liquid system (DS/S emulsion into NS), which then moves into a triphasic liquid/liquid/solid one (DS into DS/S emulsion into NS), by counter diffusion S ↔ NS.

Droplet size and mixing conditions are major determinants of where and at which speed solid growth will occur in the droplet. In large droplets, the solid growth takes place on the surface and extends in layers to the center. In small droplets, a homogeneous texture is obtained.

This article presents a complete kinetic model of these mechanisms, which show how a specific texture can be selected and the whole process controlled.

Two kinds of grains were produced and compared according to the micromeritic criteria required for direct tableting. The question of tablet cohesion is not critical with the drug we tested, and both grains are effective with regard to flowability whereas the powder produced from the standard crystallization technique is not suitable. With other drugs, a particular texture may be preferred, depending on cohesion and dissolution rate.

1. Introduction

Whether issuing from chemical or biological synthesis or extracted from natural substances, most pharmaceutical drug substances are isolated in solid form by crystallization. Generally speaking, crystallization produces fine particles (5 to 100 μm), which are in fact agglomerates of even finer crystals.

Depending on the process which the particles will undergo, particle sizes may be suitable or they may be too big or too small. If particles are too big, their surface can be reduced by crushing or by micronization. If they are too small, they can be adjusted using the particle size enlargement technique. This is particularly true for compression, when the drug substance content is high, and for microencapsulation, when the grain is coated by a protective film.

There are many different ways of obtaining grains ranging from 100 to 1500 μm. The method selected will depend on the ultimate manufacturing process retained, i.e. dry compaction, wet granulation, extrusion-spheronization, atomization, prilling, etc. In the 70s, Capes and Kawashima suggested performing particle size enlargement at the same time as crystallization (1-3), thus controlling crystal agglomeration in order to obtain large spherical grains. This was made possible by the two methods of spherical crystallization finally developed by Kawashima.

The first method is known as Spherical Agglomeration (SA) and consists of precipitating fine crys-
tals of drug substance then aggregating them using a non-miscible liquid. The second method is referred to as Emulsion Solvent Diffusion (ESD), in which a quasi-emulsion is formed by droplets of solvent containing the drug in a medium in which the drug is non-miscible, with the solvent diffusing to the outside of the droplets and into this medium. The two methods, SA and ESD, are both Spherical Crystallization (SC) techniques.

Spherical agglomerated crystals are suitable for various uses (4, 5). Their specific properties are much documented (6-11), and it is known that these microspheres show specific properties with regard to flowability and compressibility (11), sustained release (6, 7, 10), etc. These fundamentals of the SC techniques can be applied to obtain products as diverse as microcapsules (5), microballoons (7), nanospheres (9), or directly compressible products (11), thus illustrating the advantages of particles generated by SC.

Kawashima has summarized the basics of the SA and ESD methods (12, 14). A recent article further details the mechanisms of the SA method (13). The rate constant and the effect of temperature were studied (14, 15). For the ESD method, however, thermodynamic and kinetic aspects have yet to be developed to make sure that crystallization is reproducible and feasible on an industrial scale.

This article contributes to modeling the ESD method. It describes the crystallization of an acetone-soluble pharmaceutical drug substance.

2. Materials and methods

2.1 Experimental design and standard operating procedure

Figure 1 shows the apparatus used to study the ESD crystallization process. It consists of a dissolution tank (I), a pressurized flow system (II), and a crystallizer (III). Temperature control is achieved by circulating water from thermostatically-controlled baths through a double-jacket system fitted round the various parts of the unit. The two tanks have removable baffles and marine impellers for stirring. The flow rate of the drug substance solution from the dissolution tank (I) to the crystallizer (III) is controlled.

A drug substance solution is prepared in the dissolution tank (I) by dissolving a batch of the drug substance in acetone at temperature $T_1$. Double-distilled water is poured into the crystallizer (III) together with several hundred ppm of Mowiol® and maintained at temperature $T_2$. The solution is added when conditions in both tanks have stabilized.

An emulsion made up of acetone droplets saturated with the drug substance then forms in the crystallizer. These droplets quickly become spherical agglomerates consisting of a multitude of microcrystals of the drug substance. The suspension is then stirred for at least 20 minutes in the crystallizer. At the end of the procedure, the grains are removed from the bottom of the crystallizer. They are filtered using a Buchner funnel and washed with double-distilled water before drying in an oven at 50°C for 24 hours.

2.2 Products

The drug substance is a crystallized product with a purity of over 99.9%, density of $\rho_s = 1270 \pm 20$ kg/m$^3$ at 20°C, melting point at $T_m = 94.2 \pm 0.5°C$ and melting enthalpy at $\Delta H_m = 28230 \pm 250$ J/mole. The water used is double-distilled and the purity of the acetone is over 99.7%. Mowiol® is a polyvinyl alcohol used as a dispersant and supplied by Hoechst.

2.3 Drug substance solubility in acetone, water and acetone/water mixtures

Figure 2 shows the apparatus used to determine
the equilibrium of binary and ternary mixtures as a function of temperature. For the binary mixture (Figure 2(a)) the procedure is quite standard. Solutions containing an excess of solid are stirred under thermostatically controlled conditions. The saturated solutions in 25-ml flat-bottom flasks, fitted with condensers, are placed in a thermostatically controlled bath and stirred magnetically. Samples of supernatant are filtered and analyzed during the process.

With the test apparatus (Figure 2(b)), samples can be drawn from the two liquid phases of ternary mixtures without disturbing the equilibrium. It consists of a thermostatically controlled tank with six sampling points. Syringes fitted with needles are introduced into sampling points to remove samples of the liquid phases without disturbing the equilibrium.

2.4 Evaluation of physical characteristics

The conditions under which crystallization is carried out determine the texture of the grains; it is this texture which then defines the functional properties of the powder bed. In order to control the reproducibility of this process, a certain number of physical properties were evaluated. Since the material and methods are standard, they are only presented in tabular form in Table 1.

![Diagram (a) and (b)]

Fig. 2 Apparatus used for measuring liquid/liquid equilibrium (a) and liquid/liquid/solid (b) equilibrium.
(a) I-Drug substance solution II-Temperature control III-Temperature-controlled stirring tank (±0.1°C) IV-Control vessel for temperature measurements V-Magnetic stirring

### Table 1 Measurement of spherical grain properties

| Property measured | Methods |
|-------------------|---------|
| Crystal structure | X-ray diffraction |
| Density | Pycnometry |
| Apparent density | \( \rho_{\text{app}} = \frac{m_p}{V_{\text{app}}} \) |
| Tapped apparent density | \( \rho'_{\text{app}} = \frac{3}{2} \left( \frac{V_{500}}{m_p} + \frac{V_{100}}{m_p} \right) \) |
| Carr index | 100 \( (\rho_{\text{app}} \cdot \rho_{\text{app}}) / \rho'_{\text{app}} \) |
| Size distribution | Particle Size Analyzer Galai CIS1 |
| Porosity | Micromeritics Autopore II 9215 apparatus |
| Shape | Scanning Electron Microscopy |
| Flowability | Flow rate of 100g of powder in a standard funnel |
| Compaction | With 0.5% of Mg stearate in a uniaxial Frogerais A0 press Matrix: 1cm³, flat pattern of area: 11.28 cm² |

3. Results and discussion

3.1 Solubility profile

The drug substance/acetone/water ternary mixture yields a phase diagram with five regions. The Mowiol® does not penetrate the droplet under transformation so this ternary mixture is the one about to crystallize. Figure 3 shows the appearance of this diagram at 20°C.

The monophasic DS/acetone/water liquid region depicted is in equilibrium with the different phases as a function of the mass ratio of acetone in the water/acetone mixture (Ra = acetone/(water + acetone)). In region A (Ra = 1), DS is highly soluble in acetone (approximately 0.4 kg of DS/kg of solu-
bonds resulting from the presence of a certain spherical whereas in regions III and deformed, i.e. they appear slightly elongated.

Grains produced were classified into five groups by points A and B shown in Figure 4. These grains are equal in temperature $T_1$ and $T_2$ used. The difference between $T_1$ and $T_2$ is $\Delta T = T_1 - T_2$ used. The difference in temperature $\Delta T$ depends mainly on the mass ratio (Ra) and on the concentration of DS, from regions C to D, the monophasic region is in equilibrium with the biphasic liquid/solid region (crystallization of DS). In region D (Ra=0.24), the aqueous medium limits solubility to 2% so the liquid/liquid region disappears, yielding an equilibrium $L<\text{L/S}$, between regions D and E. When Ra tends toward 0, solubility decreases to 0.1% (crystallization of DS).

3.2 Grain texture
3.2.1 Grain shape, size and texture

Scanning electron microscope studies revealed that the shape and roughness of the grain surface depends mainly on the mass ratio (Ra) and on the difference in temperature $\Delta T = T_1 - T_2$ used. The grains produced were classified into five groups which are presented in Figure 4.

In regions I, II and IV of Figure 4, the grains are spherical whereas in regions III and V they are deformed, i.e. they appear slightly elongated. Sphericity decreases as the acetone: water ratio increases. Ratios exceeding 0.060 kg acetone: kg water systematically produced elongated grains. The difference in temperature may cause droplets to coalesce and grains to agglomerate in the crystallizer (region III).

Acetone: water ratios of less than 5% (Figure 4) produce grains with an internal texture characterized by several layers. Acetone: water ratios of 6% or more produce grains with a homogeneous internal texture. If the difference between $T_1$ and $T_2$ is marked ($>35^\circ C$), scanning electron microscope studies show small, spherical grains with a thick outer crust and no preferential orientation of crystals. The core is hollow (region I). These grains remain soft for a long time, indicating that a high residence time in the crystallizer is required before filtration. If there is an average difference between $T_1$ and $T_2$ (10 to 35°C), grains remain spherical, may have a hollow core, but are made up of two layers (region II). The outer crust is less dense and the surface is covered with crystals. The internal layer is very porous and the crystals are oriented towards the center. If the difference between $T_1$ and $T_2$ is less than 10°C, the outer crust is more porous and clusters of grains form (region III). Figure 5 shows the photographs of solid and hollow grains. Grain size depends on stirring conditions, the flow system and the Mowiol® concentration.

3.2.2 Internal porosity of the grains

Products prepared under the conditions represented by points A and B shown in Figure 4 were compared. A represents group II and B represents group IV. The intraparticulate volumes of A and B are equal (0.4 cm$^3$/g), but are not distributed in the same way. Product A has pore diameters over 6 μm opening into the central cavity, whereas product B pores are of smaller diameter and are more often situated in the micropore region (Table 2).

| Pore diameter (mm) | Product A | Product B |
|-------------------|-----------|-----------|
| 6 to 15 μm (macroporosity) | 0.25 | 0.10 |
| 0.2 to 6 μm | 0.10 | 0.15 |
| 0.06 to 0.2 μm (microporosity) | 0.05 | 0.15 |

The volume of mercury retained between the particles corresponds to a density of 1.10 g/cm$^3$, which is even lower than the density measured by pycnometry, but high microporosity indicates that there is a certain amount of closed porosity. After crushing, the volume of mercury indicates grains with a density of 1.22 g/cm$^3$, which is close to the triclinic crystal habitus. The disparity between

![Fig. 4](image-url)  
**Fig. 4** Grain structure as a function of the operating conditions. A and B: Operating procedure for producing grains used in tableting.
the expected result (1.27 g/cm$^3$) and the pycnometric data (1.16 g/cm$^3$) is explained by the closed porosity.

Diagrams similar to that presented in Figure 4 were prepared by Kawashima for many other substances and solvent/non-solvent combinations (19, 20). Similar results were found for all the other cases we tested. It seems possible, therefore, to make the following generalized statement: the ESD method yields three types of spherical grains (regions I, II and IV), which differ with regard to their internal structure and surface appearance. And second, two other types of grains can be obtained (regions III and V), but they are irregular and non-reproducible.

Two important questions then arise: Do these differently textured grains have different properties? And what are the kinetic aspects giving rise to these differences?

3.3 Functional properties of the grains

Once dried, all the spherical grains of the I, II, and IV groups flow freely. All Carr indices are less than 12, and all tapped apparent densities are greater than 0.50 g/cm$^3$. Table 3 shows the results for products A and B.

The size, shape, hardness and density of the spherical particles indicate good flowability. They can be coated easily because of their surface smoothness. Their size can be adapted for filling capsules or for mixing with direct tableting excipients (grain size 75-175 µm), by optimizing the stirring conditions. The flowability required for tableting is ensured.

Types I, II and IV do not differ with regard to all these points. When coating, holes which are occasionally observed on the surface of the grain are to be avoided (Figure 5).

Extensometric criteria (Table 4) were used to compare agglomerates A (hollow spheres) and B (homogeneous spheres) with powder P made up of individual crystals (5-50 µm plate-like crystals) developed using standard crystallization procedures. The matrix of the tableting machine was filled manually, since P was unsuitable for automatic filling. It was, however, possible to fill automatically with products A and B.

Tensile strength ($R_o$) was adequate (aspirin 1.0 MPa and spray-dried lactose 1.0 MPa) and sensitivity to porosity low ($\gamma < 12$), producing a tablet ($R = 0.8$) with adequate porosity ($\varepsilon = 15\%$) under
Table 4  Extensometric results

| Products | A   | B   | P   |
|----------|-----|-----|-----|
| \(R_{0}\) (MPa) | 3.8 | 4.1 | 5.6 |
| \(\gamma\)       | 10.8| 10.5| 11.5|
| \(P_y\) (MPa)   | 37  | 43  | 60  |
| \(E\) (J/g)     | 25  | 21  | 53  |
| \(P_i\) (MPa)   | 150 | 200 | 80  |

\[ R = R_0 e^{-\gamma} \]

\[ \gamma = \text{sensitivity of } R \text{ to } e \]

\[ \varepsilon = \text{porosity after relaxation} \]

\[ n = n_0 e^{-\psi} \]

\[ E = \text{specific compression energy (area of the curve } P/\text{movement)} \]

\(P_i=\text{minimum capping pressure (MPa)}\)

Moderate pressure (70 MPa). In terms of this criterion, A and B are equivalent and similar to P, suggesting that it is the molecule itself which determines cohesion. The two spherical products are plastic (\(P_y<55\) MPa), whereas the crystallized P lies between plasticity and fragility. Specific compression energy \((E)\) shows that P absorbs more energy than A and B. This energy, however, does not contribute to tablet cohesion so effectively since \(R_0\) and \(\gamma\) are similar. The minimum capping pressure \((P_i)\) at which tablets start capping confirms that P tablets are not as tough as A tablets, and A tablets are not as tough as B tablets.

Finally, the tableting profiles of A and B are quite similar. Under low pressure, the spherical grains fragment, redistribute and deform plastically. The tablet is obtained simply with no risk of capping. P crystals rearrange themselves less easily than the A and B fragments, and deform less under working pressure (70 MPa). Tablets obtained are acceptable, but tend to cap if high hardness values are required \((R=1.2 \text{ MPa})\).

The ESD method produced grains with many flaws (non-oriented crystals, microporosity, closed porosity). These flaws enable pressure to interact in a more isotropic and plastic fashion than it does with the powder obtained using the standard crystallization technique.

All the tablets of pure DS were unusable since the hydrophobic solid is practically insoluble and therefore does not dissolve well. Dissolution is the only problem related to formulation with spherical grains. There is a wide dissolution range and the problem can be solved by the addition of 5-10% of the excipients. With P, the formulation must be flowable, wettable and avoid capping. This requires a granulation procedure and the addition of 30-60% of the excipients.

4. Grain formation pattern by the ESD technique

Knowing the mechanism of grain formation should help in obtaining the chosen texture (Figure 4), in controlling surface appearance and checking for any cavities (Figure 5), and in obtaining the parameters required for optimization and scale-up of the process. Three steps are to be taken into account: droplet formation, supersaturation and crystallization of DS in droplets.

4.1 Droplet formation

Droplet size depends mainly on flow conditions, on stirring and on the surface tension between the droplet and the solution. Supposing that the droplets circulate in the continuous phase at the terminal settling velocity, it was calculated that 700-\(\mu\)m spheres circulate a hundred times quicker than 70-\(\mu\)m spheres \((8.1 \times 10^{-3} \text{ versus } 8.81 \times 10^{-5} \text{ ms}^{-1})\). Using the three-dimensionless numbers of Reynolds, Morton and Eotvos, Clift (21) determined which form a droplet takes at the terminal settling velocity. Under our test conditions as shown in Figure 6, droplets remained spherical. If surface tension is increased, droplets above 500 \(\mu\)m are subject to
deformation. Ellipsoidal or crescent shapes found in some cases by several researchers can be explained by high Reynolds and Eotvos numbers.

The movement of droplets within the medium induces circulation inside the droplets. The intensity of this internal circulation depends on the movement speed. Modeling showed that internal circulation is substantial in large droplets (450-1500 μm), less in medium-sized droplets (300-450 μm) and non-existent in small droplets (<300 μm).

4.2 Supersaturation

The drug substance is supersaturated from 20 to 25°C. Therefore cooling at (T₁ - T₂) > 30°C does not have the same effect as cooling at (T₁ - T₂) < 20°C.

Since the droplets are spherical they can be represented as a pile of n concentric crowns in which supersaturation is Sᵢ, where j = 1 on the surface, and j = n in the center. The acetone content increases with j (exit of acetone towards the exterior), and the water content decreases with j (penetration of water). The acetone: acetone+water mass ratio (Ra) increases markedly as a function of j.

When a hot droplet comes into contact with cold water, supersaturation occurs which is more marked on the surface than at the center. The solid therefore tends to appear on the surface of the droplet.

At constant temperature, DS is more soluble in acetone/water mixtures with a low water content. When water is added to the mixture (Figure 3), DS becomes less soluble. Supersaturation obtained by adding water is not possible at constant temperature for Ra between 0.7 and 1. But if the overall temperature of the droplet is decreased to temperature T, the critical Ra value is modified and it is a particular internal crown (S') which first reaches supersaturation. As a function of the size and the position of the droplet, i can include all values between 1 and n.

When internal circulation occurs in a droplet, it tends to homogenize concentration within the droplet. Supersaturation is then identical throughout and crystals will appear in a uniform fashion throughout the droplet.

4.3 Crystallization

All the possibilities are summarized in the three
4.3.1 Hollow grains with a single outside layer

Small-sized droplets (i.e. <300 μm) subjected to cooling at \((T_1 - T_2) > 35°C\) very rapidly reach a state of supersaturation where the heat transfer takes place (\(S'\)). A crust of nuclei is formed and increases by diffusion, rapidly filling any cavities. A single-layered grain with non-oriented crystals is thus formed (Type I).

4.3.2 Hollow grains with two outside layers

Larger-sized droplets (i.e. 450 μm) which undergo less rapid cooling \((T_1 - T_2 = 25°C)\) also start nucleating where the heat transfer takes place (\(S'\)). However, because circulation is quite marked, it inhibits radial diffusion and favors tangential movement, so the crystals grow at right angles to the radius until circulation is stopped (solidification) and diffusion slowed down (low porosity). Growth then changes both in direction and speed, and well-developed axial crystals form in the intermediate Si layers (Type II).

4.3.3 Homogenous grains

Large-sized droplets (>450 μm) originate from the competition between the internal circulation and acetone-water transfers. When the acetone: water ratio is high, the speeds generated by the mass transfer are higher than those generated by the internal circulation. As the mass transfer for the drug substance tested is very rapid, there is a time lag before nucleation during which internal circulation facilitates mixing within the droplet resulting in homogenization of the concentration. Under these conditions, when the nuclei appear they are well dispersed, very fine and cluster together forming a network of micropores.

4.3.4 Grain clusters and grains with cavities

Cooling at too low a temperature (difference \(T_1 - T_2 < 10°C\)) produces grain clusters (pairs of coalescent droplets). Some grains have a large cavity (Figure 5) which can be explained by coalescence: the shocks received by the coalescent grains during stirring (against the tank wall and the impellers) cause them to separate into two parts: one grain retains a cap, the other a cavity. Surface tension also influences agglomeration and cavity formation.

Finally, cooling has an effect on the roughness of the grain surface. When the temperature is high (38°C) there are no crystalline facets on the surface. When it is lower, lines appear which represent the outward growth of crystalline facets and when the temperature is low, the grains are deformed, have cavities and agglomerate.

To summarize, for a specific physicochemical system and in given hydrodynamic conditions, there is a critical grain size. Below this critical size, grains are hollow, with one or two layers depending on the difference in temperature \(T_1 - T_2\); above this critical size; they are homogeneous or have a slight hollow in the center depending on the solvent: non-solvent ratio.

5. Conclusion

The ESD spherical crystallization method developed by Kawashima is attractive because the crystallized grains produced are functional. As it is neither a purification phase nor a product-recovery phase, but a functionalization phase, it resembles granulation. However, the basic data and mechanisms involved are typically those of crystallization.

With such a polyphasic system, physicochemical complexity and related technological problems were to be feared. Amongst the solvent/non-solvent combinations suggested by Kawashima, those of acetone/water and ethanol/water are suitable for pharmaceutical purposes since they are authorized liquids and can be applied to a large number of products.

The research presented here concerns the acetone/water/DS combination and specifies the thermodynamic and kinetic bases of the technique used.

From the thermodynamic viewpoint, \(S\) (acetone) must be a very good solvent and \(NS\) (water) a non-solvent miscible in \(S\) in such a way that in the presence of the solute (DS), \(S\) emulsifies in \(NS\). By controlling surface tension and stirring, the size of the emulsion droplets can be regulated. The use of a phase diagram \(S/NS/DS\), at all working temperatures and with or without dispersant, is indispensable for this study.

From the kinetic viewpoint, the droplets quickly assume the bath temperature. The mass transfer is the following: diffusion of \(S\) in \(NS\), diffusion of \(NS\) in \(S\), circulation of \(S+DS\) inside the droplet and nucleation of \(DS\). The principal parameters are droplet size, the initial concentration of \(S\) in \(NS\), and the difference in temperature at the time \(S+DS\) are introduced into \(NS\). The area of these three dimensions covers a region with spherical crystals.
model region with deformed crystals. The spherical region subdivides into grains with hollow centers and homogeneous grains. Moreover, there are three types of solid texture around the central cavity. These various possibilities (Figures 4 and 7) are now modeled. The ESD method can be used to produce grains with a large variety of shapes, sizes (1 to 2000 μm) and internal textures.

Sizes of the order of 100 and 750 μm were tested by direct tabletting. They are spherical and contain various types of grains which can be homogeneous or hollow. For DS, these grains are all of high quality and have similar profiles. It is possible, therefore, to create conditions to optimize production and reproducibility (Figure 4, Types II or IV).

The ESD method is similar in complexity to that of crystallization. There are no particular problems concerning solid/liquid separation or drying. The formulation and tabletting process is consequently simplified.

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Nomenclature:

| Symbol | Description |
|--------|-------------|
| E      | Specific compression energy |
| Eo     | Eotvos dimensionless number (gJρd^2/σ) |
| n_s    | Powder bed mass |
| P_ρ    | Yield pressure (MPa) |
| P_1    | Minimum capping pressure (MPa) |
| R      | Tensile strength (MPa) |
| Ra     | Mass ratio of acetone in the water/acetone mixture (kg acetone per kg water/acetone mixture) |
| Re_p   | Reynolds particle number (ρ_d s U*/μ) |
| T      | Temperature (°C) |
| T_1    | Initial temperature of the dispersed phase (°C) |
| T_2    | Initial temperature of the continuous phase (°C) |
| U°     | Terminal settling velocity in the continuous phase (ms^-1) |

Greek characters:

| Symbol | Description |
|--------|-------------|
| ε      | Porosity (%) |
| μ      | Viscosity (Pa.s) |
| ρ_{app} | Apparent density of powder bed (kg/m^3) |
| ρ'_{app} | Tapped apparent density of powder bed (kg/m^3) |
| σ      | Surface tension between the droplet and the continuous phase (N/m^-1) |

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Authors' short biographies

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Dr Fabienne ESPITALIER was born in 1968. She graduated from the Ecole Nationale Supérieure de Génie Chimique of Toulouse in 1991. She prepared a PhD thesis on spherical crystallization by the quasi-emulsion technique in the Chemical Engineering Laboratory of Toulouse (UMR CNRS 5503) and obtained her doctor's degree in 1994. She is now assistant professor in the Ecole des Mines d'Albi Carmaux, in charge of crystallization research.

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Dr Béatrice BISCANS was born in 1958. She graduated from the Ecole Nationale Supérieure de Génie Chimique of Toulouse (ENSIGC) in 1982. She prepared a PhD thesis on the separation of proteins by ion exchange chromatography in the Chemical Engineering Laboratory of Toulouse (UMR CNRS 5503) and obtained her doctor's degree in 1985. She then undertook post-doctoral research on the electrophoretic separation technique. Since 1987, she has developed and supervised several studies in the field of crystallization as a researcher of CNRS (French National Scientific Centre of Research), working in the Chemical Engineering Laboratory of Toulouse (UMR CNRS 5503). In particular, her work involves the development of research studies on spherical crystallization.

Michel DELEUIL
Dr Michel DELEUIL graduated from the Chemical High School of Lyon (ESCIL). In 1968, he joined Rhône-Poulenc Company, where his work focussed on powder processes (mixing, milling, handling, drying, particle size enlargement). He was instrumental in the development of new processes such as industrial chromatography, plaster dry compaction, prilling, and electrofiltration. Since 1989, he has been in charge of pharmaceutical formulations at Rhône-Poulenc Rorer. He is co-editor of a handbook (Powder Technology and Pharmaceutical Processes, Elsevier, 1994), and associate engineer of the Rhône-Poulenc Group. He considers Dr Kawashima's studies on spherical crystallization to be particularly relevant, and initiated the present study with Dr Kawashima in the role of consultant.

Claude LAGUERIE (1947-1995*)
Professor Claude LAGUERIE died* in July 1995. He was head of the Ecole Nationale Supérieure de Génie Chimique of Toulouse (ENSIGC). During his lifetime, he developed and supervised many studies in the fields of fluidization, chemical reactor engineering, crystallization, drying and solids processing. He published more than 100 papers in international journals and also gave expert advice on spherical crystallization processes, which was also the subject of one of his last research projects.