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# Is spherical crystallization without additives possible?

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## A B S T R A C T

The quasi-emulsion solvent diffusion method of spherical crystallization consists in producing in one step crystallization and agglomeration of small crystals in droplets of an emulsion. Additives are generally used to stabilize the emulsion before crystallization. The aim of this study is to investigate the feasibility of spherical crystallization without surfactant. Experiments were performed in an automated batch laboratory scale crystallization process to study the influence of the process operating conditions on the structure of the particles obtained. The results clearly show that, for the experiments performed two types of particles are formed: primary spherical particles and secondary agglomerates. The pattern of the primary particles, observed under scanning electron microscopy, suggests that these particles result from a spherulitic crystal growth mechanism inside the droplet. The secondary agglomerates result from the agglomeration of the spherical particles. In addition, a set of experiments were performed with carefully selected solvents to study the influence of the crystallization solution/water interfacial tension, at constant hydrodynamic conditions and supersaturation level. The results of these experiments demonstrate that the interfacial tension is not a key parameter for designing such a process.

**Keywords:** Spherical crystallization; Interfacial tension; Quasi-emulsion; Agglomeration; Liquid-liquid dispersion; Spherulitic crystal growth

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## 1. Introduction

Crystallization from solution is a core technology in pharmaceutical industries. Usually, this process is a part of a wide processing system, including solid-liquid separation, particle design, formulation. As the generation step, the crystallization process determines the powder handling properties (shape, size distribution, purity, etc.). These properties affect the downstream processing. After crystallization, filtration and drying steps, the crystalline product is formulated to obtain tablets, which are the most common drug preparation. However, most of the API powders, obtained by a classical crystallization process, have poor physical properties that prevent direct tableting. To overcome these problems, a wet granulation step is added in the API solid chain production (indirect tableting). Direct tableting of API crystalline powder should enable to reduce cost and delay in the development of a pharmaceutical product. Direct tableting needs powders that excel in bioavailability, bindability, and mechanical strength.

Among the methods allowing to improve the physical properties of a crystalline powder, Kawashima et al.

(Kawashima and Capes, 1976, 1974; Kawashima et al., 1995, 2003; Kawashima and Takenaka, 1986) suggest to perform size enlargement and crystallization processes in one step. The crystals are generated and confined inside supersaturated droplets of an emulsion to form spherical particles. The possibility of forming large spherical particles directly inside the crystallizer presents many advantages for the powder processing.

The quasi-emulsion spherical crystallization process is one of the most efficient methods for performing crystallization and particles size enlargement in one step. However, this process presents two main difficulties in stirred reactor. The first one is to find the right operating conditions to form and to stabilize spherical and monodispersed droplets. The second one is to control the coexistence of solid particles and droplets to avoid coalescence and agglomeration of particles. In such a process, the structure of the final particles directly depends on the physico-chemistry properties of the compounds used and on hydrodynamics of the crystallizer.

Today the addition of small amounts of surfactants or polymers is the method usually applied to obtain the best spherical

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particles. Surfactants or polymers can decrease the interfacial tension between fluids, change the viscosity of phases and so influence the droplets sphericity and emulsion stability.

The classical process of quasi-emulsion crystallization consists in three steps: first the creation of an emulsion with a short lifetime, then an increase of supersaturation inside the droplets due to heat and mass transfer and finally, nucleation, growth and agglomeration of crystals inside the droplets. In this process, the continuous phase (generally aqueous phase) is formulated with a polymer (Mowiol, PVA, PEG), which avoids, by steric effect, secondary agglomeration. In literature, the quasi-emulsion spherical crystallization of ketoprofen was performed with mowiol 8-88 (Espitalier et al., 1997a,b,c). For ibuprofen crystallization Kachrimanis et al. (1998, 2000) described crystallization with Eudragit S100 by the solvent-change method.

Because surfactants are sometimes prohibited for toxicological reasons, the objective of this work is to study quasi-emulsion spherical crystallization without additive. When this process is performed without polymer or surfactant, agglomeration of the spherical particles previously formed and droplet coalescence may occur. In this paper, experiments have been designed to study, for a given mean droplet size, the influence of the process parameters (mixing and injected phase volume fraction) and the physico-chemical properties of the liquid phases (interfacial tension) on the morphologies of the obtained agglomerates.

## 2. Materials and methods

### 2.1. Materials

Organic solvents ethyl acetate, n-butyl acetate, methylethyl ketone (butan-2-one, MEK) and polyvinylacetate (PVA) were purchased from VWR (purity of 99.5%). The solvents were used without further purification. Double distilled water was processed through a Barnstead EASYpure UVsystem and was used as the continuous phase. The water resistivity was greater than 18 M $\Omega$  cm. Ibuprofen (C<sub>13</sub>H<sub>18</sub>O<sub>2</sub>) or (R)-(S)[2-(4-isobutylphenyl)propionic acid] was supplied by BASF.

Ibuprofen crystals belong to the space P2<sub>1</sub>/c (monoclinic system). The melting point of this colorless, crystalline material is commonly quoted as 75–77 °C (MacConnel, 1974). Molecular structure of ibuprofen is given in Fig. 1.

The physico-chemical properties of the solvents used in this study are given in Table 1 at 25 °C.

### 2.2. Spherical crystallization experiments

#### 2.2.1. Experimental setup

The experimental device, shown in Fig. 2 is composed of two elements: a pressurized reactor (for the dissolution of the API

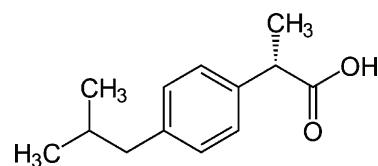


Fig. 1 – Ibuprofen molecular structure.

and the injection of the supersaturated solution) and a 2L crystallizer.

The 500 ml-pressurized reactor is a double-jacketed steel reactor. A marine propeller is used to mix the suspension. The reactor and the pouring device are thermally controlled with a precision of  $\pm 0.1$  °C. Injection of the saturated solution, from the dissolution vessel to the crystallizer, is performed by pressurization of the reactor. The pressure in the reactor is controlled to ensure a constant flow rate through the injector. The injector was a capillary tube ( $D_{ext} = 1.6$  mm,  $D_{int} = 1$  mm) and was positioned 0.5 cm above the impeller of the crystallizer.

Crystallization was performed in a round-bottomed double-jacketed glass reactor in a Labmax automated system (Mettler Toledo). The crystallizer was equipped with a lid, four baffles and a Pt-100 resistance thermometer. The precision of these thermometers is given to be 1/10 °C. The crystallizer was built according to the classical rules of batch crystallizer design ( $D_{reactor} = H_{liquid} = 14$  cm,  $l_{baffles} = 1.5$  cm). Mixing is ensured by a mixell TT propeller ( $D_p = 0.6D_{reactor} = 8$  cm). The stirrer was positioned 5 cm above the bottom of the reactor ( $h = 0.33D_{reactor} = 5$  cm).

#### 2.2.2. Experimental procedure

For all the crystallization systems studied, the experimental procedure is the same.

First, to ensure the complete dissolution of ibuprofen and to avoid clogging of the nozzle, the reactor and the pouring systems are heated 10 °C above the saturation temperature for 1 h.

The solution is then poured in the crystallizer, initially filled with water at 10 °C, with a constant flow rate during 20 s. The suspension is stirred for 15 min. Whatever the operating conditions are, the first crystals appears between 20 and 30 s after the end of the injection.

At the end of the experiment the obtained particles are recovered by filtration, washed with distilled water and dried in a ventilated drying chamber at 50 °C for 24 h.

Experiments were performed to analyze the influence of stirring rate, volume fraction of dispersed phase, pouring rate and organic phase/water interfacial tension on the morphology and size distribution of the particle obtained.

Table 1 – Physico-chemical properties of the used solvents at 25 °C.

Solvent	$\rho$ (kg m <sup>-3</sup> )	$\mu$ (mPa s)	$\gamma$ (mN m <sup>-1</sup> )	Solubility, w <sup>a</sup>	
				In water	Ibuprofen <sup>b</sup>
Butan-2-one	805	0.42	1	0.080	0.401 (0.486)
Ethyl acetate	905	0.51	6.8	0.082	0.361 (0.520)
N-butyl acetate	835	0.83	14.5	0.070	0.391 (0.531)
Water	999	1	–	–	$1.16 \times 10^{-6}$

<sup>a</sup> Mass fraction solubility from Cano et al. (2001), Garzón and Martínez (2004), and Gracin and Rasmuson (2002).

<sup>b</sup> Solubilities of ibuprofen at 40 °C are given in parenthesis.

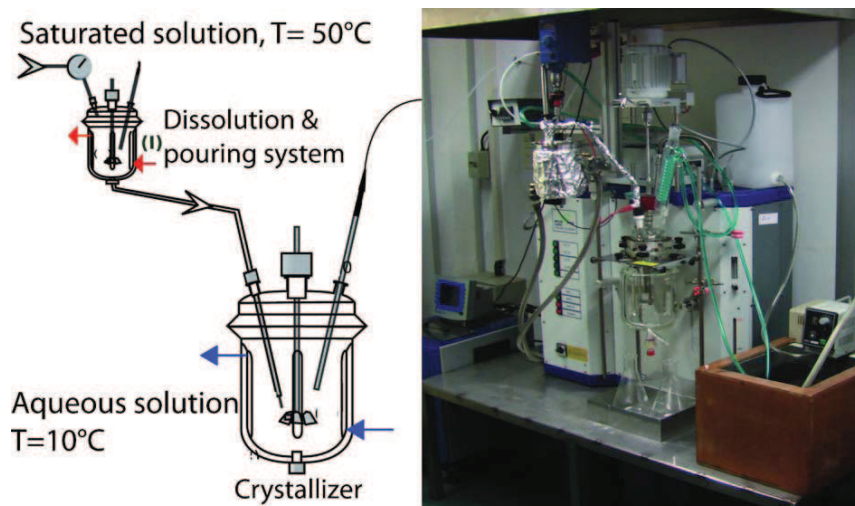


Fig. 2 – Spherical crystallization process experimental setup.

Table 2 – Process operating conditions of spherical crystallization.

Exp no.	$\phi$	$Q_C$ (ml s <sup>-1</sup> )	N (rpm)	$Pe^a$ (mW kg <sup>-1</sup> )	$M_i$ (g)	Solvent	Additive
1	2%	1.66	50	1	21.5	Ethyl acet.	–
2	2%	1.66	100	7	22.1		–
3	2%	1.66	200	157	21.3		–
4	2%	1.66	450	650	21.7		–
5	5%	4.21	50	1	55.7	Butan-2-one	–
6	5%	4.21	200	157	55.4		–
7	2%	1.66	200	157	21.7	n-Butyl acet.	1% PVA
8	2%	1.66	200	157	21.5		–
9	2%	1.66	200	157	21.3		–

<sup>a</sup>  $Pe = \rho_w N e_T N^3 D_p^5$ .

The operating conditions explored in this study are given in Table 2.

### 2.3. Solid phase characterization

The shapes of particles were examined by Scanning Electron Microscopy (LEO 435VP) operating at 5 kV or 10 kV and by reflected light microscopy (Zeiss Axio observer 20 $\times$ , 50 $\times$ ). Note that for SEM photographs, the dried agglomerates were coated with gold for 3–5 min under an argon atmosphere in a gold coating unit prior observation.

The particle size distribution of the agglomerates was obtained by sieving through four standard sieves (1.18, 1.4, 1.60 and 2 mm). For particles whose diameter is lower than 1.18 mm, a more accurate size distribution is obtained by laser diffraction particle size analyzer (Malvern Mastersizer 2000).

### 2.4. Liquid phase characterization

Interfacial tensions between organic solvents and water were measured by the dynamic Wilhemy plate method using a GBX 3S tensiometer. Time-dependent changes in the interfacial tension were detected automatically. The equilibrium inter-

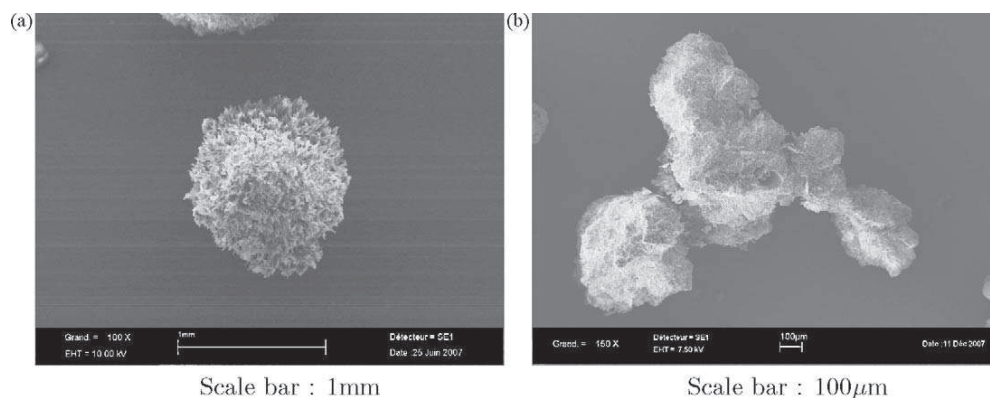


Fig. 3 – Microphotograph particles obtained in ethyl acetate/water system. (a) Spherical primary particles; (b) secondary agglomerates.

facial tension was automatically determined when a preset of standard deviation (0.1 mN/m) was reached. The temperature of the system was controlled and maintained at 25 ° C by a cooling circulating oil bath. The beaker was filled with 70 ml of water saturated with organic solvent. The entire plate was then immersed in the aqueous phase and then 10 ml of organic solvent was carefully deposited on the surface of the aqueous phase. By measuring the applied force according to the immersion depth and the dimension of the substrate perimeter, the contact angle can be calculated using the relationship:

$$\gamma = \frac{F}{L \cos \theta} \quad (1)$$

where  $\gamma$  is the contact angle,  $F$  the measured force,  $L$  the wetted perimeter (40 mm) and  $\theta$  the contact angle.

### 3. Results and discussion

In this work, the influence of the process operating conditions (stirring rate, volume fraction of dispersed phase) and the influence of the physico-chemical properties of the liquids (interfacial tension, nature of the crystallization solvents and additives) on the morphologies of the agglomerates have been studied. For the whole set of experiments performed (except for n-butyl acetate), two types of particles were obtained. Representative SEM microphotographs of the particles obtained are given in Fig. 3.

The primary particle (Fig. 3a) results from spherical crystallization process within each droplet. The secondary agglomerates (Fig. 3b) results from an agglomeration process of primary particles. Depending on the operating conditions and on the nature of the liquid phases used, different proportions of each type of particles are obtained.

**Table 3 – Mean sizes and mass fractions of spherical primary particles obtained.**

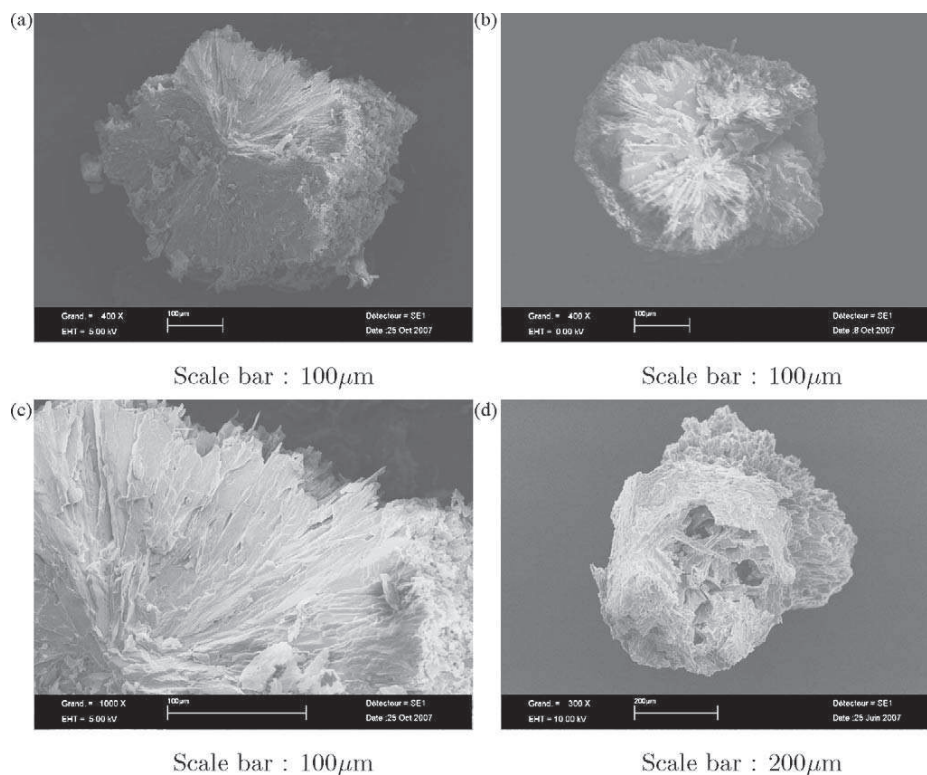
Exp no.	$d_M$ ( $\mu\text{m}$ )	$d_{\text{initial}}$ ( $\mu\text{m}$ )	$W_{pp}$
1	775 ( $\pm 50$ )	953	0.27
2	940 ( $\pm 95$ )	1150	0.15
3	880 ( $\pm 90$ )	1080	0.19
4	719 ( $\pm 60$ )	885	0.17
5	–	–	0
6	–	–	0
7	715 ( $\pm 40$ )	865	0.39
8	712 ( $\pm 20$ )	861	1
9	–	–	0

#### 3.1. Characterization of the spherical primary agglomerates

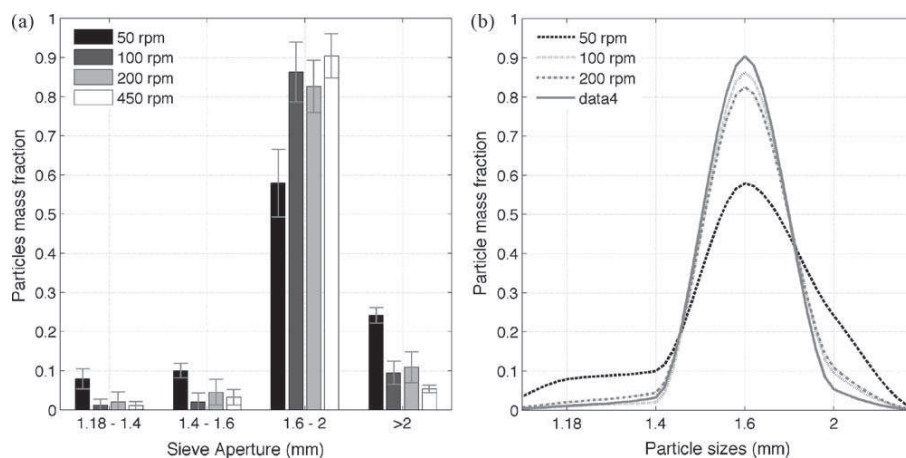
##### 3.1.1. Influence of the process operating conditions

The experimental results in terms of mean particle size, measured by laser diffraction, and the mass fraction of primary particles are reported in Table 3. In this table, it can be noticed that when n-butyl acetate is used as crystallization solvent, it was impossible to obtain spherical primary particles. In the vessel the agglomerates are actually spherical but they are soft and sticky and their structure is lost during the downstream processes (filtration and drying). In addition, in the range of operating conditions tested, when no additive is added to the water phase, it was impossible to obtain only individual spherical particles.

The diameter of the spherical particles directly depends on the initial droplets diameter which depends on hydrodynamics of the crystallizer (mixing and pouring rates) and on the physico-chemical properties of the liquids. The sizes of the primary spherical particles, reported in Table 3, are always lower than the internal capillary diameter which is



**Fig. 4 – Microphotograph of broken primary particles.**



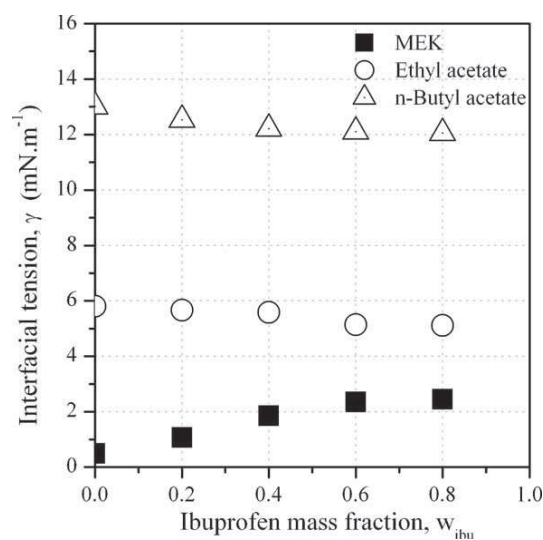
**Fig. 5 – Particle sizes distribution for different stirring rates in ethyl acetate/water system. (a) Experimental size distribution; (b) interpolated sizes distribution.**

due to the shrinking of the droplet during crystallization. The initial droplet diameter can be roughly calculated, under the assumption that all ibuprofen crystallizes in the droplet to form a non-porous particle, by the following relation:  $d_{initial} = d_M / \phi_{ibu}^{1/3}$ . Where  $\phi_{ibu} = V_{ibu} / V_{drop}$  is the ibuprofen volume fraction inside the droplet (deduced from the ibuprofen solubility). The obtained hypothetical initial droplet diameters are reported in Table 3.

### 3.1.2. Morphology of primary spherical particles

In quasi-emulsion crystallization processes, the general explanation of particle enlargement is nucleation of many crystals within each organic drop that agglomerate into dense object. However in our case, the long induction time observed during the experiments (around 30s) indicates a low nucleation rate which should give a moderate number of crystal within each droplet. This observation is incompatible with the agglomeration process generally claimed for the spherical crystallization process. In addition, whatever the crystallization solvent used, the particles obtained present a radiating pattern, as shown for a broken primary particles in Fig. 4. This pattern is typical of spherulitic crystal growth. In addition, to support this mechanism, two “uncrystallized eyes” characteristic of spherulitic crystal growth can be observed in Fig. 4d.

This mechanism produces space filling spherical polycrystalline objects growing from a central seed by radial non-crystallographic branching (Goldenfeld, 1987). However, considering the possibility of ibuprofen to induce a liquid-liquid phase separation (LLPS) before crystal nucleation (observed under microscope and by He et al., 2007) it is impossible to state that it is droplet (from LLPS) as in the case of l-glutamic acid (Roelands et al., 2007) or non-crystallographic



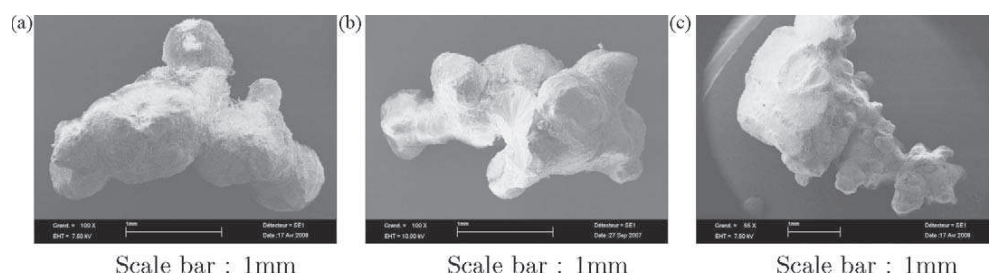
**Fig. 7 – Organic phase/water interfacial tension as a function of the mass fraction of ibuprofen introduced in the solvent.**

branching of acicular crystals (Beck et al., 2009; Andreassen, 2005) that initiate spherulitic crystal growth of ibuprofen.

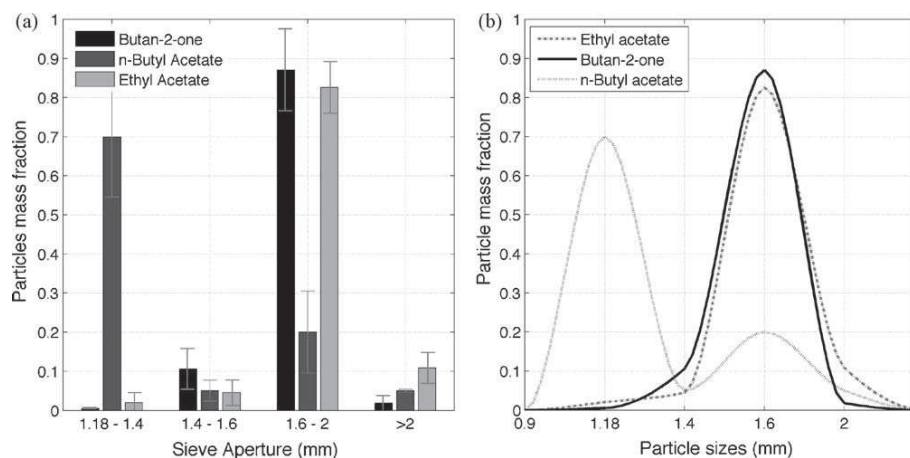
## 3.2. Influence of the process operating conditions on the formation of secondary agglomerates

### 3.2.1. Influence of the stirring rate

The results obtained in terms of particles size distributions (PSD) for a stirring rate ranging from 50 to 450 rpm (experiments 1–4) are given in Fig. 5 for four sieve apertures.



**Fig. 6 – Microphotograph of secondary agglomerates. (a) 100 rpm; (b) 200 rpm; (c) 450 rpm.**



**Fig. 8 – Particle sizes distribution for different crystallization solvents. (a) Experimental size distribution; (b) interpolated sizes distribution.**

The size enlargement process in stirred vessel is a complex mechanism which is a balance between particles agglomeration and breakage. The results, presented in Fig. 5b, show that when the stirring rate is increased, the PSD is narrower.

As shown in Fig. 6, the structure of the agglomerates obtained is the same for all the experiments performed. These particles show a loose structure characteristic of a process limited only by the meeting probability of particles, and thus by the collision frequency of particles (similar to the diffusion limited aggregation mechanism). Indeed ibuprofen is highly hydrophobic which gives rise to strong attractive interaction between particles and in order to reduce the free energy of the system, the hydrophobic particles tend to be in contact with each other.

In addition, the remaining uncrystallized solution (crystallization solvent and dilute ibuprofen) acts as a binding agent which covers the particles, and promotes the agglomeration efficiency. Then, the crystallization of ibuprofen creates solid bridges between particles.

### 3.2.2. Influence of the dispersed phase volume fraction

To increase the yield of the crystallization process it seems reasonable to increase the volume fraction of the introduced dispersed phase up to the miscibility limit of the organic phase in the aqueous phase. The experiments nos. 5 and 6 have been performed by injecting 5% of the organic phase. In the range of the operating conditions tested, when the concentration of the organic phase is close to the saturation of the liquid phase, the particles are soft (gel like structure) and sticky. As a consequence, during the process, the particles stick to the impeller and to the crystallizer wall. The gel like structure is obtained when the mass transfer from the organic phase to the aqueous phase is too slow (Kawashima et al., 1995; Nocent et al., 2001). The lifetime of the emulsion is then much higher which leads to an increase of the coalescence frequency of the droplets.

### 3.2.3. Influence of the crystallization solvent

As the agglomeration process is a complex mechanism, in order to study the influence of the interfacial tension between the crystallization solvent and water, the crystallization solvents were carefully chosen. The selected solvents have a significant difference in interfacial tension with water and have roughly the same physico-chemical properties

(density, viscosity, ibuprofen solubility and miscibility with water).

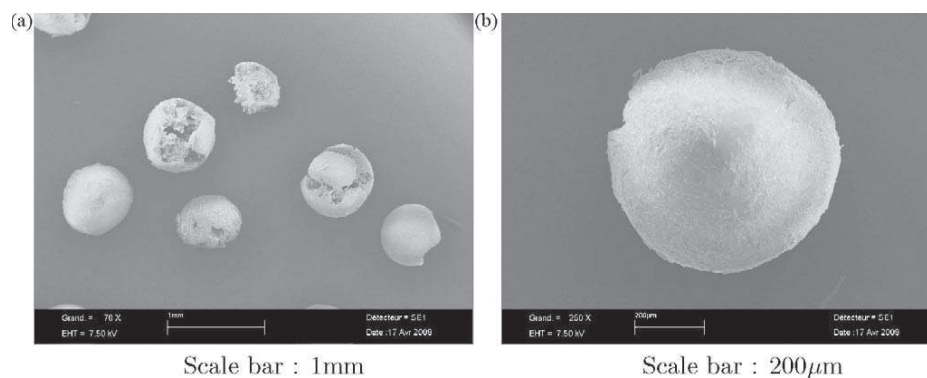
**3.2.3.1. Interfacial tension measurements.** The measured interfacial tension at the pure organic solvent/water interface ranged from  $0.5 \pm 0.1$  for butan-2-one to  $13.0 \pm 0.9$  mN/m for n-butyl acetate. When the measurements were performed with organic phase containing ibuprofen, the solvent/water interfacial tension varied with the mass fraction of ibuprofen introduced. To be sure that the scale of interfacial tension values is not modified by the addition of the solute, measurements of interfacial tension between water and organic solvent with different concentrations (up to the solubility) of ibuprofen were performed. The equilibrium interfacial tensions values are plotted against the mass fraction of ibuprofen introduced in Fig. 7.

The results show that for ethyl acetate and n-butyl acetate, the interfacial tension decreases with increasing the amount of ibuprofen. On the contrary, for butan-2-one the interfacial tension increases when increasing the amount of ibuprofen. The ibuprofen and the organic solvent molecule will compete for the interface based on their interfacial activity. The contribution of each component of the organic phase in the interfacial energy will affect the stability of the system. Therefore, the introduction of ibuprofen in the solvent stabilizes the organic phase/water system. In the case of MEK, the reverse is observed. Nevertheless, the interfacial tension scale is maintained when ibuprofen is added to the organic solvent, i.e.:

$$\gamma_{\text{MEK/water}} < \gamma_{\text{Acet/water}} < \gamma_{\text{n-but/water}}$$

**3.2.3.2. Influence of the organic solvent-water interfacial tension of secondary agglomeration.** The reduction in the interfacial free energy of an emulsion system contributes to the emulsion stability. This means that reducing the interfacial energy between the organic solvent and the water would reduce droplets coalescence and secondary agglomeration. A set of experiments was performed with different organic solvents for the same hydrodynamic conditions ( $N = 200$  rpm) and at constant volume fraction of dispersed phase ( $\phi = 2\%$ ). The results obtained in terms of particles size distribution are presented in Fig. 8.

As already mentioned, when n-butyl acetate is used as the crystallization solvent (experiment no. 9), it was impossible to obtain spherical primary particles. In fact, due to the



**Fig. 9 – Microphotograph of particles obtained in water-PVA systems.**

high interfacial tension between n-butyl acetate solution and water, the generated droplets are large and tend to coalesce to form larger droplet, which is incompatible with the spherical crystallization process. On the contrary, when butan-2-one is used as the crystallization solvent (experiment no. 8), the proportion of fully spherical agglomerates obtained is increased by 200% in comparison to the process using ethyl acetate (cf. Table 3). As expected, the rate of secondary agglomeration process is greatly decreased.

In addition, to show that interfacial energy is not the key parameter for designing such a process, classical spherical crystallization experiments were performed by adding a polymer to the aqueous phase (experiment no. 7). The water phase was formulated in a way that the interfacial tension of the system ethyl acetate/water-PVA (0.1%) was the same as for the butan-2-one/system. The SEM photographs of the particles obtained are shown in Fig. 9. This figure and the results of the mass fraction of primary particles obtained given in Table 3 clearly show that, when a polymer is added to water (i.e. for the same interfacial tension energy and a slightly increase in the viscosity of the aqueous phase), the secondary agglomeration process is totally suppressed by steric effects.

#### 4. Conclusion

The experiments performed in this study allow to reveal the different mechanisms during a quasi-emulsion spherical crystallization process without additives. Indeed, whatever the operating conditions are, two types of agglomerates are obtained: primary spherical agglomerates whose size is determined by the capillary diameter, and secondary agglomerates resulting of the agglomeration of the spherical primary particles.

On the contrary of what have been observed for other spherical quasi-emulsion crystallization processes, the results obtained in this study suggest that the formation of the primary spherical particles results from spherulitic crystal growth mechanism and not from a agglomeration of fine crystals in the droplet.

In addition, even if the agglomeration process is a very complex mechanism, thanks to the experiments performed with different solvents and with polymer, it can be stated that the interfacial tension is not the key parameter to consider for designing such a process.

So, the answer to the question: “is spherical crystallization without additive possible?” is no for ibuprofen (and probably for other hydrophobic compounds) in the range of operating conditions tested. It is shown, in this study, that for

totally avoiding agglomeration of primary particles, the aqueous phase has to be properly formulated.

#### Nomenclature

$\gamma$	interfacial tension (mN/m)
$\phi_{ibu}$	ibuprofen volume fraction
$\phi$	dispersed phase volume fraction
$\rho_w$	suspension density ( $\text{kg m}^{-3}$ )
$d_{initial}$	initial droplet size ( $\mu\text{m}$ )
$d_M$	primary spherical particles mean size ( $\mu\text{m}$ )
$D_{int}$	internal capillary diameter (mm)
$D_p$	propeller diameter (m)
$M_i$	injected ibuprofen mass (g)
$N$	stirring rate (rpm)
$Ne_T$	power number of the propeller
$Pe$	power input ( $\text{mW kg}^{-1}$ )
$Q_C$	pouring rate ( $\text{ml s}^{-1}$ )
$V$	droplet volume (ml)
$W_{pp}$	primary spherical particles mass fraction

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#### References

- Andreassen, J.-P., 2005, Formation mechanism and morphology in precipitation of vaterite-nano-aggregation or crystal growth? *J Cryst Growth*, 274(1/2): 256–264.
- Beck, R., Malthe-Srensens, D. and Andreassen, J.-P., 2009, Polycrystalline growth in precipitation of an aromatic amine derivative and l-glutamic acid. *J Cryst Growth*, 311(2): 320–326.
- Cano, H., Gabas, N. and Canselier, J.P., 2001, Experimental study on the ibuprofen crystal growth morphology in solution. *J Cryst Growth*, 224(3/4): 335–341.
- Espitalier, F., Biscans, B., Authelin, J.-R. and Laguerie, C., 1997, Modelling of the mechanism of formation of spherical grains obtained by the quasi-emulsion crystallization process. *Chem Eng Res Des*, 75(2): 257–267, industrial crystallization.
- Espitalier, F., Biscans, B. and Laguerie, C., 1997, Particle design. Part A: nucleation kinetics of ketoprofen. *Chem Eng J*, 68(2/3): 95–102.
- Espitalier, F., Biscans, B. and Laguerie, C., 1997, Particle design. Part B: batch quasi-emulsion process and mechanism of grain formation of ketoprofen. *Chem Eng J*, 68(2/3): 103–114.

- Garzón, L.C. and Martínez, F., 2004, Temperature dependence of solubility for ibuprofen in some organic and aqueous solvents. *J Solution Chem*, 33(11): 1379–1395. Nov.
- Goldenfeld, N., 1987, Theory of spherulitic crystallization. *J Cryst Growth*, 84(4): 601–608.
- Gracin, S. and Rasmuson, A.C., 2002, Solubility of phenylacetic acid, p-hydroxyphenylacetic acid, p-aminophenylacetic acid, p-hydroxybenzoic acid, and ibuprofen in pure solvents. *J Chem Eng Data*, 47(6): 1379–1383.
- He, G., Tan, R.B.H., Kenis, P.J.A. and Zukoski, C.F., 2007, Generalized phase behavior of small molecules and nanoparticles. *J Phys Chem B*, 111(43): 12494–12499.
- Kachrimanis, K., Ktistis, G. and Malamataris, S., 1998, Crystallisation conditions and physicochemical properties of ibuprofen-eudragit s100 spherical crystal agglomerates prepared by the solvent-change technique. *Int J Pharm*, 173(1/2): 61–74.
- Kachrimanis, K., Nikolakakis, I. and Malamataris, S., 2000, Spherical crystal agglomeration of ibuprofen by the solvent-change technique in presence of methacrylic polymers. *J Pharm Sci*, 89(2): 250–259.
- Kawashima, Y. and Capes, C., 1974, An experimental study of the kinetics of spherical agglomeration in a stirred vessel. *Powder Technol*, 10: 85–92.
- Kawashima, Y. and Capes, C., 1976, Further studies of the kinetics of spherical agglomeration in a stirred vessel. *Powder Technol*, 13: 279–288.
- Kawashima, Y., Cui, F., Takeuchi, H., Niwa, T., Hino, T. and Kiuchi, K., 1995, Parameters determining the agglomeration behaviour and the micromeritic properties of spherically agglomerated crystals prepared by the spherical crystallization technique with miscible solvent systems. *Int J Pharm*, 119: 139–147.
- Kawashima, Y., Imai, M., Takeuchi, H., Yamamoto, H., Kamiya, K. and Hino, T., 2003, Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. *Powder Technol*, 130: 283–289.
- Kawashima, Y. and Takenaka, H., 1986, Development of agglomerates process by using a flocculation phenomenon of particle in liquid and the application to pharmaceutical system. *Hyomen Kagaku*, 22: 719–728.
- MacConnel, J.F., 1974, 2-(4-Isobutylphenyl) propionic acid. *Cryst Struct Commun*, 3: 973–975.
- Novent, M., Bertocchi, L., Espitalier, F., Baron, M. and Couarraze, G., 2001, Definition of a solvent system for spherical crystallization of salbutamol sulfate by quasi-emulsion solvent diffusion (quesd) method. *J Pharm Sci*, 90(10): 1620–1627.
- Roelands, C.P.M., ter Horst, J.H., Kramer, H.J.M. and Jansens, P.J., 2007, Precipitation mechanism of stable and metastable polymorphs of l-glutamic acid. *AIChE J*, 53(2): 354–362. URL: doi:10.1002/aic.11072