Definition of a solvent system for spherical crystallization of salbutamol sulfate by quasi-emulsion solvent diffusion (QESD) method

M Nocent, L Bertocchi, Fabienne Espitalier, Michel Baron, G Couarraze

Definition of a Solvent System for Spherical Crystallization of Salbutamol Sulfate by Quasi-Emulsion Solvent Diffusion (QESD) Method

M. NOCENT,[1] L. BERTOCCHI,[1] F. ESPITALIER,[2] M. BARON,[2] G. COUARRAZE[3]

[1]GlaxoSmithkline Laboratories, Pharmaceutical Development Department, Zone Industrielle n°2, 23 Rue Lavoisier, 27000 EVREUX, France

[2]Ecole des Mines d'Albi-Carmaux, Centre Poudres et Procédés, Laboratoire de Génie des Procédés des Solides Divisés, UMR 2392 CNRS, Campus Jarlard, Route de Teillet, 81013 ALBI CT Cedex 09, France

[3]Laboratoire de Physique Pharmaceutique, URA CNRS 1218, Faculté de Pharmacie de Paris Sud, 5 rue JB Clement, 92290 CHATENAY MALABRY, France

ABSTRACT: In this paper we describe how the spherical crystallization process by QESD method can be applied to a water-soluble drug, salbutamol sulfate. The type of solvent, antisolvent, and emulsifier and the concentration of emulsifier to be used for the production of spherical particles with a size range 80–500 μm are determined. Furthermore, the solvent/antisolvent ratio and the temperature difference between them (ΔT) are studied . It was observed that, in the case of salbutamol sulfate, the ΔT value has no influence on the formation of spherical particles. A very large metastable zone of salbutamol sulfate in water could explain this phenomenon. Finally, the influence of emulsifier concentration and of maturation time on the size of spherical particles is studied. The results show that these two parameters must be fixed to control the size of the recovered particles.

Keywords: spherical crystallization; QESD method; spherical particles; salbutamol sulfate; emulsifier

INTRODUCTION

Taking physical properties of powders into consideration from the synthesis stage can optimize them, facilitate formulation, and reduce costs and delays in the development of a pharmaceutical product. In this context, the spherical crystallization process, by which spherical particles can be produced, may be attractive as because it can lead to significant improvements in the physical properties of materials. Previous studies have shown improvements in terms of flowability,[1] compressibility, and compactibility.[2,3] Formulation experiments have also been carried out to incorporate additives during the process to modify the dissolution rate of the drug in aqueous solution.[4]

Two spherical crystallization techniques have been defined and studied in the past: the spherical agglomeration method[5] and the quasi-emulsion solvent diffusion method (QESD). It is the latter process we study in this work.

The QESD method was first mentioned in 1989,[2] and is illustrated in Figure 1. The solvent

M. Nocent's present address is Laboratoires GlaxoSmithkline, DPE, Zone Industrielle n°2, 23 Rue Lavoisier, 27000 EVREUX, France.

Correspondence to: M. Nocent (Telephone: 00 (33) 2 32 23 55 00; E-mail: mn64067@glaxowellcome.co.uk)

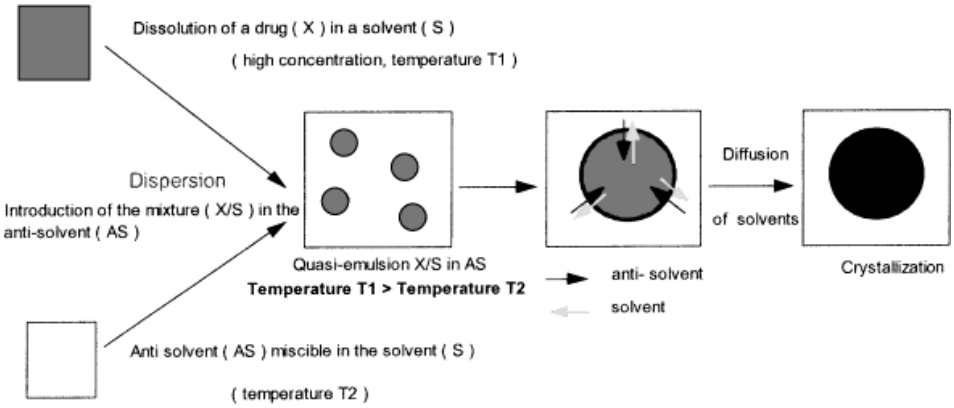

Figure 1. Presentation of spherical crystallization process by QESD method.

phase (drug dissolved in solvent) and the antisolvent phase (antisolvent and emulsifier) are prepared separately and maintained at different temperatures. The solvent solution is then added to the antisolvent solution under agitation. The interactions between drug and solvent being stronger than the interactions between solvent and antisolvent, the solvent is dispersed in the antisolvent and creates a quasi-emulsion. The formation of this unstable emulsion is induced by the increase in the interfacial tension between solvent and antisolvent. However, an emulsifier needs to be used.[6] As soon as the emulsion is formed, the solvent and antisolvent diffuse in opposite directions. The antisolvent diffuses into the droplets, reduces the solubility of the drug, and induces its crystallization inside the droplets.[7,8] Crystallization is frequently facilitated by maintaining a temperature difference (ΔT) between the solvent and antisolvent. Then, spherical agglomerates of crystals are formed, which are typically called spherical particles.

The aim of the present study was to select a solvent system for salbutamol sulfate for which there have been no previous studies. Thus, the first objective was to select the right solvent, antisolvent, and, if necessary, emulsifier to obtain salbutamol sulfate spherical particles. In a second step, the spherical crystallization process itself was studied to define what variables influence the formation of spherical particles. Finally, the processing variables influencing the particle size distribution were examined. The tendencies observed in this study must subsequently be confirmed using pilot plant equipment, which will be part of another work.

MATERIALS AND METHODS

Materials

Salbutamol sulfate (GlaxoWellcome) is (*RS*)-1-(4-hydroxy-3-hydroxymethylphenyl)-2-(*tert*-butylamino)ethanol sulfate. The pK_a of its phenol group is 9.4 and the pK_a of its amine group is 10.0. Ethyl acetate (Merck), ethanol (Carlo Erba), acetone (Merck), Abil EM90 (polysiloxan polyalkyl polyether copolymer, Goldschmidt AG), Lutrol F127 (Poloxamer 407, BASF), diethanolamine (BASF), Montane 20 (sorbitan monolaurate, SEPPIC), ammonium chloride (Merck), ammonium acetate (Prolabo), and ammoniac (Prolabo) were used. All reagent qualities were of analytical grade (99.5% minimum).

Methods

To optimize the yield of the process, the selection criteria of the solvent was a solubility value of salbutamol sulfate > 0.1 g/g. Different selection criteria were applied for the antisolvent. It had to be miscible or partially miscible with solvent in the proportions used. The solubility of salbutamol sulfate in antisolvent should be < 100 μg/g at low temperatures ($\sim 5^\circ$C) to reduce losses of the drug at the end of the process. The last two selection criteria concern the formation of an emulsion when the saturated solvent is poured into the antisolvent and the crystallization of the drug into the droplets of the emulsion.

Salbutamol Sulfate Solubility Studies

The solubility of salbutamol sulfate was studied in three antisolvents (ethanol, acetone, and ethyl

acetate) at 5°C. For water (solvent), solubilities were measured at six temperature levels ranging between 5 and 60°C. Three experiments were carried out at each temperature.

Suspensions containing excess salbutamol sulfate in solvent or antisolvent were continuously stirred for 48 h at fixed temperature. The suspensions were then filtered on Acrodisc 0.45 μm filters. In the case of water and ethanol, the mass of salbutamol sulfate present in a known mass of filtrate was then determined by drying in an air oven, at ~40°C, to a constant weight. This temperature was used to avoid drug degradation during drying. It was observed that heating the drug at 50°C in an oven for more than one day caused the powder to become yellow colored. In the case of acetone and ethyl acetate, the salbutamol sulfate recovered was dissolved in a known volume of water, and the concentration was measured by ultraviolet (UV) spectrometry at 276nm. The methodology here differs because of low concentration values in acetone and ethyl acetate.

Determining the Width of the Metastable Zone

Salbutamol sulfate (46.5 g) and water (150 g) were introduced in a double-jacket reactor. The solution was kept under magnetic stirring and heated at 60°C until dissolution. The solution was then gradually cooled to 5°C. In parallel, conductivity was regularly recorded. Two experiments with different cooling rates (10 and 20°C/h) were carried out.

Spherical Crystallization Trials

Salbutamol sulfate was dissolved in water at the desired temperature to form a saturated aqueous solution. At the same time, the emulsifier (quantity dependent on the type of emulsifier used) was added to the antisolvent. The antisolvent solution was maintained at 5°C. When two emulsifiers were used, one was added to the solvent solution and the other to the antisolvent solution. The aqueous solution, while still being stirred, was then poured with a syringe into the antisolvent solution (Figure 2). The dispersion was kept agitated for 30 min, and the solid particles (when formed) were recovered by filtration, washed with pure ethyl acetate, and then dried in an oven at 30°C.

The water temperature ranged between 25 and 45°C depending on the temperature difference studied (ΔT between 20 and 40°C). The

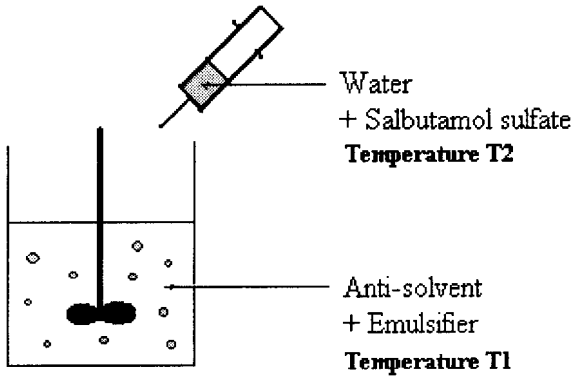

Figure 2. Material used for spherical crystallization trials.

concentration of the salbutamol sulfate in aqueous solution was therefore dependent on the water temperature and varied between 0.23 and 0.28/g. When the influence of the solvent/antisolvent ratio is studied, the water and antisolvent weights are changed to keep the total weight constant (100 g).

The agitator type was a marine propeller (Janke and Kunkel RW10R). The agitation speed was 510 rpm.

The influence of emulsifier concentration and of maturation time on the spherical particle size distribution was studied. The maturation time is defined as the time that the spherical particles were kept under stirring after their formation. Two maturation times were tested: 135 and 30 min. Two emulsifier concentrations were compared: 0.2 and 1.0%.

Median particle diameter and span values were determined by laser diffraction (Malvern Multisizer type S 300 RF; size range, 0.05–900 μm). The dispersing solvent was isooctane.

The shape and texture of the particles were observed by scanning electron microscopy (SEM) under vacuum (Hitachi S3200N).

RESULTS AND DISCUSSION

Definition of the Solvent System for QESD Method

Solubility Studies

Stability studies of salbutamol sulfate in water showed that no chemical degradation of salbutamol sulfate occurred in aqueous solution for 16 h at temperatures < 60°C. Accordingly, the solvent

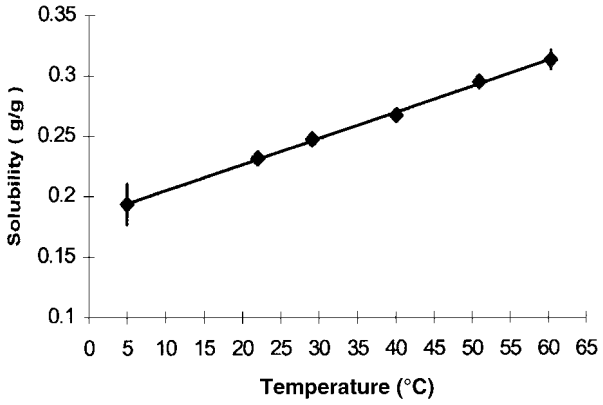

Figure 3. Solubility of salbutamol sulfate in water versus temperature.

solution can be heated at these temperatures during solubility studies and spherical crystallization experiments.

The results of solubility determination in water are illustrated in Figure 3. The solubility values showed reproducibility from ~1 to 9% around the mean value. The 9% value was obtained for the 5°C trial. The fact that filtration was carried out at ambient temperature could explain this high value. The solubility (S, g/g) increased linearly with the temperature (T, °C) according to the following equation:

$$S = 0.0022T + 0.1828 \quad (1)$$

Trials to increase salbutamol sulfate solubility by using solvents different from water (e.g., a buffer solution with a pH value that increases the ionization level of the molecule) were unfruitful. Water was therefore finally chosen as the appropriate drug solvent for our study.

The results of solubility determination in the three potential antisolvents are given in Table 1. The high coefficients of variation can be explained by the very low solubility values obtained, notably in acetone and ethyl acetate. It appears that salbutamol sulfate is more soluble than expected in ethanol, whereas solubility values in acetone and ethyl acetate are lower than the specified selection criteria (100 μg/g). Acetone and ethyl acetate were thus retained for further spherical crystallization trials.

Table 1. Solubility of Salbutamol Sulfate in Potential Antisolvents at 5°C

Parameter	Ethanol	Acetone	Ethyl acetate
Solubility at 5°C (μg/g)	754.2	37.3	5.9
Coefficient of variation (%)	7.8	11.9	20.1

Choice of Antisolvent by Spherical Crystallization Trials

In preliminary studies, two variables were chosen as spherical crystallization parameters: the solvent/antisolvent ratio ($Ra = 0.01$) and the temperature difference between solvent and antisolvent ($\Delta T = 30°C$).

The use of acetone or ethyl acetate as an antisolvent brought about the crystallization of salbutamol sulfate during the process. For both, an emulsifier was required to form an emulsion (see Table 2). Finally, using Montane 20 as an emulsifier, only ethyl acetate gave visual evidence of both emulsification and crystallization inside droplets. Acetone was therefore not selected as an antisolvent.

Using ethyl acetate as an antisolvent, emulsification was noted as soon as the aqueous solution of salbutamol sulfate was introduced in the ethyl acetate. A crystallization phase inside droplets began a few seconds after the emulsification phase. Nevertheless, the droplets rapidly coalesced, and sticky agglomerates with a gel-like structure were formed. Kawashima et al. obtained such a structure in one of their studies.[2] This phenomenon could be explained by a desorption of surfactant molecules from the droplet interface, a rupturing of droplets, and a precipitation of surfactant from the newly formed water/ethyl acetate solvent mix. A comparison of the solubility parameters [δ, $(cal/cm^3)^{1/2}$] of sorbitan monolaurate ($\delta = 8.4$), ethyl acetate ($\delta = 9.1$), and water ($\delta = 23.4$) showed that sorbitan monolaurate is much less soluble in a water/ethyl acetate mix than in ethyl acetate.[9,10]

Ethyl acetate is thus considered as an appropriate antisolvent, whereas other trials are necessary to fix the type and percentage of emulsifier to use.

Choice of Emulsifier Type and Concentration

Spherical crystallization experiments were carried out with different types and different concentrations of emulsifiers, using a range of HLB (hydrophilic/lipophilic balance) values between 5 and 27. Two independent variables were fixed for

Table 2. Spherical Crystallization Trials for Antisolvent Choice

	Emulsification/ Crystallization	Acetone	Ethyl Acetate
Miscibility with water	—	Miscible	Miscible for ratio < 4 g of water for 100 g of solution
Spherical crystallization without emulsifier	Emulsification	−	−
	Crystallization	+	+
Spherical crystallization with Montane 20 (5% m/m)	Emulsification	−	+
	Crystallization	+	+

each experiment: $Ra = 0.01$ and $\Delta T = 30°C$. All trials and results are detailed in Table 3.

When a hydrophilic emulsifier was used (Lutrol F127, HLB = 27), an emulsification phase was observed but no crystallization occurred. Introducing a hydrophilic surfactant in the less polar phase of an emulsion could result in a phase inversion of the emulsion, as reported by Lin et al.[11] The emulsion visually observed in this case could therefore be an ethyl acetate-in-water emulsion in which salbutamol sulfate, staying in the continuous (aqueous) phase, could not crystallize.

Using different types, concentrations, and HLB values of hydrophobic surfactants also gave some negative results. These results were obtained because of high instability in the primarily formed emulsion. The formation of gel-like structures could have the same origin as that already explained.

Spherical particles were obtained using Abil EM90 (HLB = 5) at 0.2% (2 mg/g). The stabilizing properties of this emulsifier can be explained as follows: polysiloxane chains are placed at the solvent–antisolvent interface, polyether chains are dissolved in water, and polyalkyl chains are dissolved in ethyl acetate.

Scanning electron micrographs of the spherical particles are shown in Figure 4. The micrographs show hollow spherical particles with smooth surfaces. The median spherical particle size [$D(v,0.5)$] and a sphere size distribution parameter ($\text{Span} = [D(v,0.9) - D(v,0.1)]/D(v,0.5)$) are shown in Table 4 (sample A).

Having shown the feasibility of the process on salbutamol sulfate, we went on to study the influence of relevant parameters on the formation of spherical particles. Secondly, the influence of processing variables on the particle size and the size distribution was elucidated.

Influence of Processing Variables on the Formation of Spherical Particles

In previous studies, several authors have shown the importance of Ra and ΔT on the process.[2,12] In fact, the crystallization of the drug inside the droplets is only possible because of the mass transfer (diffusion of solvent and antisolvent in opposite directions) and the heat transfer

Table 3. Spherical Crystallization Trials for Emulsifier Choice

Emulsifier (In Ethyl Acetate/ in Water)	Percentage (w/w)	HLB	Spherical Particles	Observations
Lutrol F127/Diethanolamine	0.045/1	27	−	Emulsification/ crystallization
Montane 20	1	8.6	−	Gel-like structure
	3	8.6	−	Gel-like structure
	5	8.6	−	Gel-like structure
Abil EM90/Lutrol F127	1.0/0.05	6.0	−	Gel-like structure
	1.5/0.05	5.7	−	Gel-like structure
	2.5/0.05	5.4	−	Gel-like structure
Abil EM90	0.2	5.0	+	—
	1.5	5.0	−	Gel-like structure

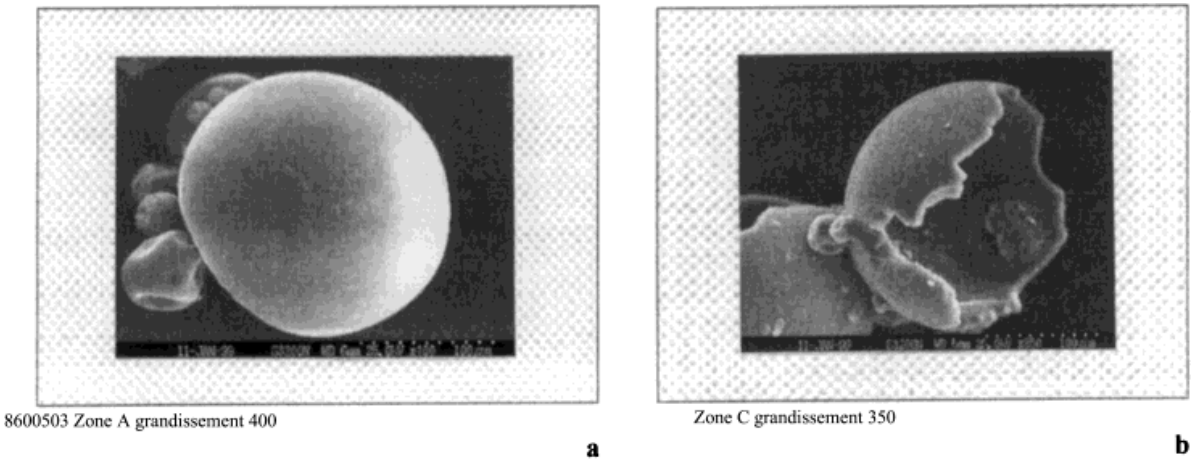

Figure 4. Scanning electron micrographs of spherical particles obtained by the quasi-emulsion process: (a) spherical particle; (b) hollow sphere.

(difference of temperature between solvent and antisolvent). An Ra/ΔT diagram has therefore been plotted, and the different types of particles obtained by varying these two parameters are illustrated by Figure 5.

Three regions were found. Spherical particles (region I) were formed for low ratio values ($Ra \leq 0.01$) and a temperature difference $> 25°C$. Sticky agglomerates with gel-like structure (region II) were obtained for $Ra = 0.01$ and $\Delta T = 25°C$. Using high ratio values ($Ra > 0.01$), no solid particles were recovered (region III). No emulsification phase was observed visually. At these ratios, surfactant molecules probably form aggregate structures like micelles in the solvent mix. A colloidal dispersion would thus be obtained.

In most cases similar results were obtained for different values of ΔT. Thus, there seemed to be no influence of heat transfer, which could be due to the specific crystallization properties of salbutamol sulfate in water. Accordingly, the metastable zone was determined using two different cooling rates. No apparition of crystals in solution all along the cooling process, whatever was the cooling rate applied, was observed visually. Moreover, the conductivity values remained stable. The metastable zone is therefore $> 50°C$. It was noted that the cooling rates applied during these experiments were much lower than those effectively occurring during spherical crystallization trials. However, previous results showed that wider metastable zones are obtained by increasing cooling rates.[13] It may thus be taken that the temperature difference between solvent and antisolvent cannot cause crystallization of salbutamol sulfate. It may therefore be supposed that, for this drug, the crystallization is mainly the consequence of the solvent diffusion inside and outside the droplets.

Influence of Processing Variables on the Size of Particle Spheres

The particle size distribution of the powder obtained by using an emulsion concentration of 1.0% was determined and compared with that obtained with a concentration of 0.2%. The results

Table 4. Mean Size and Size Distribution of Spherical Particles Synthesized With Different Parameters

Parameter	Sample A	Sample B	Sample C
Emulsifier concentration	0.2%	1.0%	0.2%
Maturation time	30 min	30 min	135 min
Type of distribution	Monomodal	Monomodal	Monomodal
$D(v,0.5)$	187 μm	168 μm	287 μm
Span	1.088	1.878	1.260

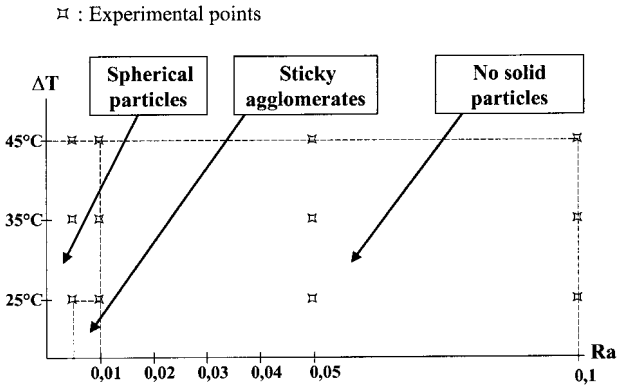

Figure 5. Ra/ΔT diagram of the water/salbutamol sulfate/ethyl acetate/Abil EM90 system.

are illustrated in Table 4 (Samples A and B). Using a 1.0% value rather than 0.2% leads to a slightly lower median particle size. On the other hand, the size distribution is wider (Span = 1.878) using a 1.0% value. The emulsifier concentration would probably influence the final particle size in modifying the initial droplet mean size and size distribution.

The size distribution of the powder made using a maturation time of 135 min was determined and compared with that obtained with a maturation time of 30 min. The results are illustrated in Table 4 (Samples A and C). It is seen that the median diameter increases with an increase in the maturation time. This result could be explained by an agglomeration of particles over time. Hunter reported a mechanism of flocculation of a dispersion caused by polymer molecules dissolving in the continuous medium.[14] So-called "bridging flocculation" was observed at low polymer concentrations and is considered to be a consequence of the adsorption of the segments of polymers onto the surface of more than one particle.

CONCLUSION

Experiments performed to select a quasi-emulsion crystallization system for producing spherical particles of salbutamol sulfate gave the following combination: water (solvent)/ethyl acetate (antisolvent)/Abil EM90 (emulsifier). It was shown that the Ra parameter has an influence on the formation of spherical particles. On the other hand, similar results are obtained in most cases despite varying the ΔT values. The fact that a very large metastable zone was found for salbutamol sulfate in water could explain this phenomenon. The emulsifier concentration and maturation time were shown to have an influence on the size of spherical particles obtained. These tendencies will now need to be confirmed at a higher scale and optimization will be applied. Attention will then be focused on the physicochemical and mechanical properties of the spherical crystals.

REFERENCES

1. Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K. 1994. Improvements in flowability and compressibility of pharmaceutical crystals for direct tabletting by spherical crystallization with a two-solvent system. Powder Technol 78: 151–157.
2. Kawashima Y, Takeuchi H, Niwa T, Hino T, Yamakoshi M, Kihara K. 1989(c). Preparation of spherically agglomerated crystals of an antibacterial drug for direct tabletting by a novel spherical crystallization technique. Congr Int Technol Pharm 5th(3):228–234.
3. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. 1992(a). Hollow microspheres for a use as a floating controlled drug delivery system in the stomach. J Pharm Sci 81(2):135–140.
4. Ribardiere A, Tchoreloff P, Couarraze G, Puisieux F. 1996. Modification of ketoprofen bead structure produced by the spherical crystallization technique with a two-solvent system. Int J Pharm 144:195–207.
5. Kawashima Y. 1984. Development of spherical crystallization technique and its application to pharmaceutical systems. Arch Pharm Res 7(2): 145–151.
6. Kawashima Y. 1994. New process: Application of spherical crystallization to particulate design of pharmaceuticals for direct tabletting and coating and new drug delivery systems. In: Chulia D, Deleuil M, Pourcelot Y, editors. Handbook of powder technology, Powder technology and pharmaceutical process, volume 9. Chapter 14. Amsterdam: Elsevier, pp. 493–512.
7. Morishima K, Kawashima Y, Kawashima Y, Takeuchi H, Niwa T, Hino T. 1993. Micromeritic characteristics and agglomeration mechanisms in spherical crystallization of bucillamine by the spherical agglomeration and the emulsion solvent diffusion methods. Powder Technol 76:57–64.
8. Espitalier F, Biscans B, Authelin J-R, Laguerie C. 1997. Modeling of the mechanism of formation of spherical grains obtained by the quasi-emulsion crystallization process. Inst Chem Eng 75(a):257–267.
9. Kon-no K, Kitahara A, El Seoud OA. 1987. Micelle formation and catalysis in Nonaqueous media. In:

Nonionic surfactants: Physical chemistry; Surfactant sciences series, Vol 23. New York: Marcel Dekker, Chapter 4, pp.185–231.
10. Grulke EA. 1976. Solubility parameters values. In: Polymer handbook, Third edition. New York: John Wiley & Sons, Inc., pp. 519–559.
11. Lin TJ, Kurihara H, Ohta H. 1975. Effects of phase inversion and surfactant location on the formation of O/W emulsions. J Soc Cosmet Chem 26:121–139.
12. Espitalier F, Biscans B, Laguerie C. 1997. Particle design. Part B: Batch quasi-emulsion process and mechanism of grain formation of ketoprofen. Chem Eng J 68:103–114.
13. Mullin JW. 1993. Metastable zone widths. In: Crystallization, third edition. Oxford, UK: Butterworth-Heinemann. pp. 189–193.
14. Hunter RJ. 1987. Polymeric stabilization and flocculation. In: Foundations of colloid science, Volume 1. Oxford: Clarendon, Chapter 8, pp. 450–493.