ELSEVIER

International Journal of Pharmaceutics 173 (1998) 61–74

international journal of pharmaceutics

Crystallisation conditions and physicomechanical properties of ibuprofen–Eudragit® S100 spherical crystal agglomerates prepared by the solvent-change technique

K. Kachrimanis, G. Ktistis, S. Malamataris *

Laboratory of Pharmaceutical Technology, Department of Pharmacy, University of Thessaloniki, Thessaloniki 54006, Greece

Received 5 January 1998; received in revised form 21 May 1998; accepted 31 May 1998

Abstract

Spherical crystal agglomeration of ibuprofen was performed in the presence of Eudragit® S100 using the solvent-change (ethanol–water) method and applying different crystallisation conditions such as initial supersaturation under both increasing and constant drug:polymer ratios and different rates of stirring and cooling. The temperature in the crystallisation liquid and water consumption were recorded to determine the effects of polymer presence on crystallisation parameters (drug loading efficiency, crystal yield and mean 'apparent crystal growth' rate) and to correlate them with the physicomechanical properties of the agglomerates. It was found that crystal yield and drug loading efficiency are not affected by the crystallisation conditions, while the mean 'apparent crystal growth' rate increases with initial supersaturation ratio and stirring rate; however, the cooling effect is stirring dependent, probably due to changes in the nucleation mechanism. The particle size of agglomerates decreases, while sphericity, surface roughness and intraparticle porosity increase with polymer presence. Also, particle size and sphericity decrease, while intraparticle porosity increases with initial supersaturation. The effects of Eudragit® addition on the fundamental particle properties are attributed to the habit and growth rate changes of ibuprofen microcrystals, as well as to their coating before binding into spherical agglomerates. The stirring rate effect on particle size is enhanced by slow cooling, and sphericity becomes maximal at slow cooling and fast stirring. The size and sphericity changes due to stirring and cooling are attributed to the polymer binding ability and to detachment of small fragments from the agglomerate surface. Flow or packing behaviour and densification of agglomerates at low compression are determined by the sphericity changes and their yield pressure by the brittleness due to the incorporated polymer. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: 'Apparent crystal growth' rate; Compression behaviour; Eudragit® S100; Ibuprofen; Micromeritic properties; Spherical crystallisation

* Corresponding author. Tel.: +30 31 997651; fax: +30 31 997652; e-mail: smalam@pharm.auth.gr

0378-5173/98/$ - see front matter © 1998 Elsevier Science B.V. All rights reserved.
PII S0378-5173(98)00191-4

1. Introduction

Spherical crystallisation is a technique used in the production of spherical agglomerates consisting of microcrystals for the improvement of the flowability and compactibility of drugs and the control of their rate of release (Kawashima et al., 1982). Spherical crystallisation is achieved either by the formation of an unstable organic solvent emulsion and subsequent diffusion of the solvent through the emulsion droplet interface and evaporation to the environment (emulsion solvent diffusion method), or by the addition of a poor solvent to a solution of a drug (SC, solvent-change method).

Ibuprofen is a non-steroidal anti-inflammatory drug, slightly soluble in water (≈ 1 mg/ml at 22°C), with poor flow and compaction properties due to its needle-like (acicular) crystal shape and viscoelastic behaviour, respectively (Marshall et al., 1986). It is used in the therapy of rheumatoid arthritis and osteoarthritis in high doses: 1800–3200 mg daily or 200–800 mg every 4–6 h as a single dose. Eudragit® S100 is an anionic copolymer based on methacrylic acid and methylmethacrylate (ratio 1:2). It is soluble in water at $pH > 7$ and is therefore used as an enteric coating material which is resistant to the gastric fluid. In the last 15 years, the use of Eudragit® S100 has been investigated extensively in drug formulations: for example, in the preparation of enteric drug delivery systems containing 5-amino salicylic acid or steroids (Dew et al., 1982) and prednisolone (Ford et al., 1992), in the microencapsulation of ketoprofen (Goto et al., 1988), in the preparation of furosemide microspheres (Akbuga, 1989), and in the enteric coating of microspheres containing diclofenac and sodium carboxymethylcellulose (Arica et al., 1996). The SC method has been used for the preparation of solid dispersions of dipyridamole in Eudragit® S100 (Beten et al., 1992), and spherical crystallisation has been employed particularly for the preparation of ibuprofen microspheres by the quasi-emulsion solvent diffusion method (Kawashima et al., 1989) and recently by the SC method (Kislalioglou et al., 1991, Khan et al., 1994).

It is known that crystallisation techniques provide a route towards the control of the characteristics of pharmaceutical raw materials to such an extent that the properties of powders can be optimised to suit particular processing applications. Therefore, in the present work, spherical crystallisation of ibuprofen was performed in the presence of Eudragit® S100 by employing the SC method and applying different crystallisation conditions, such as initial degree of supersaturation under both increasing and constant drug:polymer ratios, as well as different stirring and cooling rates. The aim was to investigate the mechanism of microsphere formation and the effects of the above crystallisation conditions on the 'apparent crystal growth' rate, the crystal yield and the drug loading efficiency, as well as on physicomechanical properties such as size, shape, surface roughness, density, porosity and compression behaviour of the resultant spherical crystal agglomerates.

2. Materials and methods

2.1. Materials

The materials used in this study were: ibuprofen in crystalline form (USP grade; Boots Pharmaceuticals, Nottingham, UK; supplied by Vianex, Athens, Greece), and the acrylic polymer Eudragit® S100 in powder form (supplied by Röhm Pharma, Darmstadt, Germany) as main constituents; all-glass distilled water and analytical grade absolute ethanol (Merck, Darmstadt, Germany) as poor and good solvent, respectively; and mercury (Merck, Darmstadt, Germany) as the displacement liquid for the porosity determination.

2.2. Spherical crystallisation

The apparatus shown diagrammatically in Fig. 1 was used for the spherical crystallisation and the following procedure was applied. A certain amount of ibuprofen (35–80 g) and polymer (3.5–8.0 g) were dissolved in 100 g of ethanol, kept under constant agitation and temperature (50°C), inside a 1000-ml (7×30 cm) crystallisa-

tion vessel. Then distilled water was added (700 ml), at a selected rate, using a peristaltic pump (Desaga, Heidelberg, Germany). At the same time, the solution of drug and polymer was cooled from 50°C down to 10°C with a Julabo refrigerated circulator and temperature programmer (type PRG1; Julabo Labortechnik, Seelbach, Germany). The spherical crystal agglomerates produced were collected by vacuum filtration, dried at 50°C in a vacuum oven to constant weight and kept in screw-capped amber-glass jars.

Seven batches of spherical agglomerates were prepared under constant stirring (600 rpm) and cooling (0.33°C/min) by employing different initial supersaturation and both increasing and constant drug:polymer ratio and one batch of ibuprofen crystals without the presence of Eudragit® S100 (blank or reference sample). Nine more batches of agglomerates were prepared employing a constant drug:polymer ratio (80/8 g), three different stirring rates (300, 600 and 900 rpm) and three cooling rates (0.66, 0.33 and 0.22°C/min).

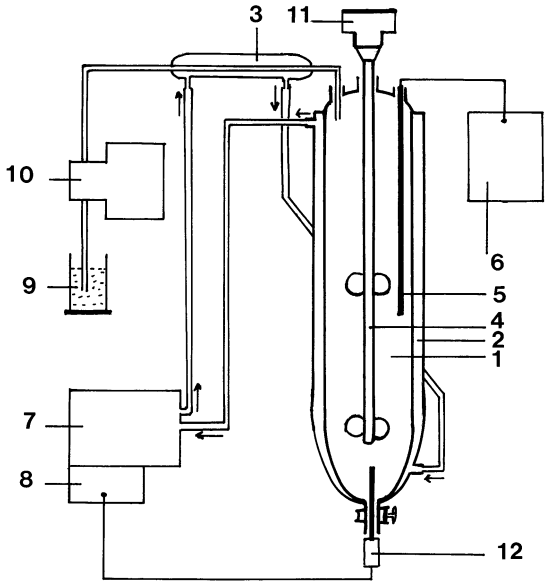

Fig. 1. Apparatus used for the spherical crystallisation of ibuprofen: 1, 1000-ml (7 × 30 cm) crystallisation vessel; 2,3, double-sided jacket; 4, stirring paddle; 5, thermocouple; 6, chart recorder; 7, refrigerated circulator; 8, temperature programmer; 9, water tank; 10, peristaltic pump; 11, motor; 12, thermistor.

2.3. Crystal yield and 'apparent crystal growth' rate

Crystal yield was calculated from the weight of spherical crystal agglomerates produced and is expressed as a percentage of the total weight of drug and polymer dissolved initially in the crystallisation solution.

Crystal growth rate was expressed as 'apparent crystal growth' since it was indirectly determined from the total amount of ibuprofen contained in the agglomerates produced divided by the duration of temperature deviation in the crystallisation medium. Temperature deviation was recorded using a copper–constantane thermocouple connected to a chart recorder (Knauer, 2.5 mV, 120 mm/h). The onset, maximum and endset of deviation from the programmed temperature were noted and the duration of positive deviation was considered as the crystallisation time, since it originates from the exothermic nature of crystallisation.

2.4. Characterisation of spherical crystal agglomerates

The physicomechanical properties affecting the quality of tablets and capsules produced from spherical crystal agglomerates (i.e. particle size and size distribution, shape, density and porosity) were evaluated. Also, scanning electron photomicrographs were taken in order to investigate the morphology and structure of the agglomerates. Drug loading efficiency, as well as flow (angle of repose) or packing (compressibility index, CI) and compression (Heckel's equation parameters) behaviour were assessed.

2.4.1. Size

Geometric mean diameter (d_g) and geometric standard deviation (σ_g) were determined by sieve analysis of 30-g samples shaken for 15 min on a series of test sieves (Endecotts, London, UK).

2.4.2. Shape

Particle shape was characterised using an image processing and analysis system (Quantimet 500; Leica, Cambridge, UK). Samples were transferred

to a slide, dispersed in paraffin oil and 'roundness', a shape factor which is equal to the square of the perimeter divided by 12.56 times the projection area, was determined for at least 200 particles; it assumes the value of 1 for a sphere with an ideal circular projection.

2.4.3. Surface roughness

Surface roughness was characterised on the basis of the fractal dimension, D_f, determined in the Quantimet 500 image analysis system with a successive dilation sequence. D_f was determined by increasing the measuring unit of the projected perimeter (Flook, 1978) and calculating the surface and length of the perimeter. From the slope of logarithmic plots of perimeter length versus the measuring unit ('Richardson' plots), D_f was obtained as: $D_f = 1 + |\text{slope}|$.

2.4.4. Density

True density (ρ_g) was measured on an air comparison pycnometer (Beckman Model 930). Loose bulk density (ρ_b) and tapped density (ρ_t) were measured in a volumeter (Model JEL ST 2; J. Engelsmann, Ludwigshafen, Germany) using a 50-ml cylinder. The packing ability during tapping is expressed as Carr's compressibility index (Carr, 1965): $\text{CI}\ (\%) = [(\rho_t - \rho_b)/\rho_t] \times 100$.

2.4.5. Porosity

The pycnometric method of Strickland et al. (1956) was used for porosity measurements with 3-g samples. The volume of mercury in the pycnometer was measured at different intrusion pressures between 360 and 1200 mmHg, which correspond to a pore diameter range of about 40–12 μm calculated by Washburn's equation: $Pd = -4\gamma\cos\theta$, where P is pressure, d is pore diameter, γ is surface tension of mercury (0.48 MN^{-1}) and θ is the contact angle of mercury with solid materials (140°). Particle density, interparticle porosity (ϵ_{inter}, %), total intraparticle porosity (ϵ_{intra}, %) and the fractions of intraparticle pores between 40 and 12 μm (ϵ_{12-40}) and < 12 μm ($\epsilon_{<12} = \epsilon_{intra} - \epsilon_{12-40}$), as well as the mean diameter of intraparticle pores were calculated.

The particle density (ρ_{p360}) was obtained from the weight of spherical agglomerates in the pycnometer and the volume of mercury replaced by them at 360 mmHg intrusion pressure. Interparticle porosity (ϵ_{inter}, %) was obtained from tapped (ρ_t) and particle density (ρ_{p360}) values: $\epsilon_{inter}\ (\%) = (1 - \rho_t/\rho_{p360}) \times 100$. The total intraparticle porosity (ϵ_{intra}, %) was obtained from particle density (ρ_{p360}) and true density (ρ_g) values: $\epsilon_{intra}\ (\%) = (1 - \rho_{p360}/\rho_g) \times 100$. The fraction of intraparticle pores between 40 and 12 μm (ϵ_{12-40}) was obtained from the difference in mercury volume replaced between 360 and 1200 mmHg and that of pores < 12 μm from the difference $\epsilon_{intra} - \epsilon_{12-40}$. The mean diameter of intraparticle pores (d_{pm}) is the size corresponding to 50% cumulative intraparticle pore oversize obtained from plots of ϵ_{intra} versus pore diameter. Three measurements were made on each batch and mean values were calculated.

2.4.6. Scanning electron microscopy

A very thin coat of carbon was applied to samples of dry spherical crystal agglomerates before being examined using a scanning electron microscope (JSM 840A; JEOL, Japan). Photomicrographs were taken of each sample at different magnifications.

2.4.7. Angle of repose

This was determined using the method described by Pilpel (1964). Five determinations were made for each batch and the mean value was computed.

2.4.8. Compression behaviour

Samples giving a 3-mm thick compact, at zero porosity, were weighed accurately ($\pm$ 0.1 mg) and compressed at pressures up to 120 MPa on an instrumented single-punch tabletting machine (type KIS; Kilian, Köln-Niehl, Germany) equipped with a 13-mm diameter die and flat-faced punches. Before each compression experiment, the die and punches were lubricated with compressing magnesium stearate powder. A load cell of the foil strain-gauge type (LFH-71 subminiature load cell; RDP Electronics, Wolverhampton, UK) and a linear displacement transducer (GTX 5000, RDP 1166) connected to an S-7 DC and an E309 (RDP Electronics) am-

plifier were used for the measurement of the upper punch force and displacement, respectively. Electric signals obtained for pressure and displacement were fed into a computer through a Handyscope polymeter (TP208, 12 bits, 20 MHz; TiePie Engineering, The Netherlands) used in the transient recorder mode and collected simultaneously. The number of measurements captured during each compression cycle was about 1000. The collected data were transferred to Excel program, and the packing fraction (p_f = bulk density/true density) was calculated from tablet thickness, after correction for the elastic deformation of punches and other parts of the tabletting machine. Profiles of log reciprocal porosity ($\log[1/(1-p_f)]$) versus applied pressure were constructed according to Heckel's equation (Heckel, 1961), and yield pressure (P_y) of the samples was calculated from the slope of the linear part of the plots.

2.4.9. Drug loading efficiency

Samples of spherical crystal agglomerates (≈ 20 mg) were accurately weighed and dissolved in 20 ml of ethanol. The ibuprofen content was assayed spectrophotometrically at 246.5 nm, using the calibration curve $Y = 0.70957X + 0.03604$, where Y is the concentration of ibuprofen and X is absorbance. The polymer does not interfere with the assay at this wavelength. Drug loading efficiency is the ratio of the experimentally measured ibuprofen content to the theoretical value expressed as a percentage. Five samples were examined for each batch of spherical agglomerates. Uniformity of drug loading efficiency was also evaluated from drug content analyses in five sieve fractions of each microsphere batch and is expressed as the standard deviation (S.D.).

3. Results and discussion

3.1. Crystallisation parameters

Results of crystallisation parameters such as drug loading efficiency, crystal yield, points of temperature deviation in the crystallisation liquid, water consumption at maximum deviation and mean 'apparent crystal growth' rate are given in Tables 1 and 2 for the spherical crystal agglomerates prepared under different initial supersaturation and stirring or cooling, respectively.

3.2. Drug loading efficiency and crystal yield

For all the crystal agglomerates prepared, drug loading efficiency (Tables 1 and 2) slightly exceeds the theoretically expected value (100%) and is not affected either by the initial supersaturation or by

Table 1
Crystallisation parameters (drug loading efficiency, crystal yield, points of temperature deviation, water consumption at maximum temperature deviation and mean 'apparent crystal growth' rate) for spherical crystal agglomerates prepared with different supersaturation ratios

Ibuprofen:Eudragit® ratio (g/g)	Loading efficiency mean (S.D.) (%)	Crystal yield (%)	Temperature deviation (°C)			Water consumption (ml)	'Apparent crystal growth' (g/min)
			Onset	Maximum	Endset		
80/0.0	100.0 (0)	94	37.8	39.9	29.6	295	2.6
35/3.5	102.3 (2.2)	94	34.9	36.2	30.6	270	2.4
50/5.0	102.3 (4.9)	95	34.9	36.2	30.7	310	3.0
65/6.5	102.3 (1.9)	96	37.2	38.4	33.1	320	3.7
80/8.0	102.3 (3.4)	95	38.1	38.4	31.5	305	3.4
65/8.0	102.8 (1.0)	99	37.8	38.3	30.8	295	3.2
50/8.0	102.9 (0.2)	93	36.1	37.0	30.6	285	2.4
35/8.0	103.2 (1.1)	91	34.9	35.4	30.4	265	2.1

Table 2
Crystallisation parameters for spherical crystal agglomerates prepared at constant ibuprofen:Eudragit® ratio (80/8 g) employing different cooling and stirring rates

Stirring rate (rpm)	Cooling rate [a] (°C)	Loading efficiency mean (S.D.) (%)	Crystal yield (%)	Temperature deviation (°C)			Water consumption (ml)	'Apparent crystal growth' (g/min)
				Onset	Maximum	Endset		
300	0.22	101.2 (1.7)	98	35.1	36.0	28.9	295	2.4
600		101.2 (1.9)	94	36.9	39.5	32.1	260	2.5
900		101.2 (3.2)	93	38.1	40.6	31.7	220	2.7
300	0.33	104.5 (1.5)	96	35.2	36.4	26.4	320	2.6
600		102.3 (3.4)	95	38.1	37.4	29.5	305	3.4
900		101.2 (2.0)	91	34.3	36.4	29.0	330	4.6
300	0.66	102.3 (1.1)	93	33.5	36.0	24.2	320	3.2
600		102.3 (1.4)	95	35.1	38.3	26.3	290	3.3
900		101.2 (1.2)	97	35.9	39.2	27.0	280	3.4

[a] Cooling rates of 0.22, 0.33 and 0.66°C/min correspond to water addition rates of 3.9, 5.8 and 11.6 ml/min, respectively.

the changes in stirring and cooling rate. The small increase observed is probably caused by the relative amounts of polymer and ibuprofen remaining dissolved in the crystallisation liquid. Also, the drug loading results do not show differences greater than 5% between the different sieve fractions of agglomerates examined, indicating uniform distribution of constituents. Furthermore, the crystal yield results do not show significant differences due to changes either in the initial supersaturation (Table 1) or in the stirring and cooling rate (Table 2). The most probable explanation for this could be the completion of crystal formation long before the end of cooling, as is evident from the temperature versus time plots of crystallisation liquid (Fig. 2).

Fig. 2 represents a typical plot of temperature in the crystallisation liquid versus time. A straight line corresponds to the programmed temperature and the positive deviation is due to heat released during phase transition of ibuprofen. For all the crystallisation experiments the onset, the maximum and the endset of temperature deviation or crystallisation process can be seen. Onset and endset points should correspond to initiation and cessation of crystallisation, respectively, while the point of maximum temperature deviation corresponds to maximum crystal growth rate (i.e. maximum supersaturation ratio).

3.3. Temperature deviation and water consumption

The results in Table 1 show that the points of temperature deviation and the water consumption at maximum temperature deviation increased slightly as the amount of ibuprofen added to the

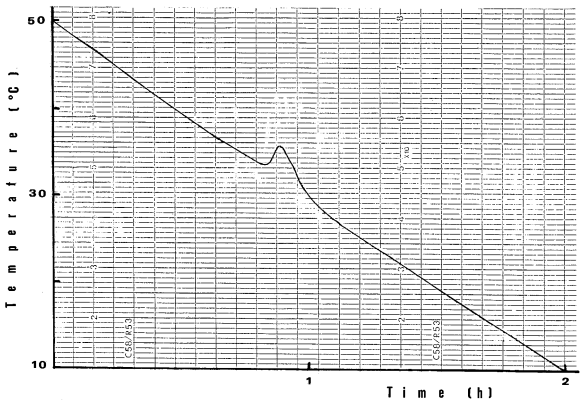

Fig. 2. Typical temperature versus time plot for the spherical crystallisation of ibuprofen in the presence of Eudragit® S100 (80/8 g), at 900 rpm and 0.33°C/min cooling rate.

crystallisation liquid is increased. Furthermore, differences in the temperature deviation points and water consumption can be noticed between the reference sample and the spherical agglomerates prepared with the same amount of ibuprofen in the presence of Eudragit® (ibuprofen:Eudragit® 80/8). All these indicate that crystallisation initiates when the supersaturation ratio reaches a critical value due to cooling and water addition, which should be affected by the amount of ibuprofen and the presence of Eudragit® S100 in the crystallisation liquid.

The effect of stirring and cooling rate on the points of temperature deviation is shown in Table 2 and it is not simple and general. The points increase and the water consumption decreases as the stirring rate is increased, except for the cases of intermediate cooling rate (0.33°C/min), in which the temperature deviation points reach maximum and the water consumption a minimum value at an intermediate stirring rate (600 rpm). Also, water consumption is inversely related to the points of temperature deviation, as is to be expected. Assuming that the temperature deviation points are related to the width of the metastable zone and the increase of deviation onset indicates earlier initiation of crystallisation, meaning a narrower metastable zone (Mullin, 1993), we can conclude from the results in Table 2 that the width of the metastable zone decreases with stirring at the cooling rates of 0.22 and 0.66°C/min, while at the intermediate cooling rate (0.33°C/min) it reaches minimum value at 600 rpm.

3.4. 'Apparent crystal growth' rate

The results for mean 'apparent crystal growth' rate (Tables 1 and 2) show that it increases, as expected, with the initial supersaturation and, furthermore, with the stirring rate (Table 2). The stirring effect seems to be independent of cooling rate employed and in agreement with Mullin's suggestion that stirring contributes to a decrease of the metastable zone width, because it facilitates nucleation and crystal growth. Furthermore, stirring may contribute to nucleation due to the dispersion of primary crystals or their fragments (secondary nucleation). This may result in the increase of the crystal growth rate observed, which seems to be maximal at the intermediate cooling rate (0.33°C/min).

Regarding the combined effect of stirring and cooling on the mean 'apparent crystal growth' rate, from the results in Table 2 it can be seen that at 300 rpm the crystal growth rate increases with the cooling rate, while at 600 and 900 rpm it shows maxima at the intermediate cooling rate (0.33°C/min). A possible reason for this might be the minimisation of secondary nucleation with low stirring, resulting in predominance of cooling rate as a factor of nucleation and crystal growth, while at higher stirring rates secondary nucleation might take place and the cooling rate is no longer the predominant factor for nucleation.

3.5. Physicomechanical properties

Experimental results for micrometric properties, namely geometric mean diameter (d_g), geometric standard deviation (σ_g), roundness and fractal dimension (D_f), are given in Tables 3 and 4, together with the packing or flow parameters, such as bulk and tapped density, CI and angle of repose. The results of true and particle density are given in Tables 5 and 6, together with the porosity and compression behaviour parameters.

3.5.1. Size

From the particle size results (Table 3), it can be seen that, for the reference sample, the geometric mean diameter (d_g) is slightly higher than that of agglomerates prepared in presence of polymer using the same amount of ibuprofen (ibuprofen:Eudragit® 80/8). Also, in general, the value of d_g decreases with the initial supersaturation ratio, except for the case of drug:polymer ratio 35/8. Assuming that the polymer improves binding of developed ibuprofen microcrystals into spherical crystal agglomerates and that ibuprofen in higher concentration increases the number of microcrystals and therefore the frequency of collisions between them, it is expected that the value of d_g will increase with both initial supersaturation and polymer addition. Therefore, the unexpected size decrease should be combined with the geometric

Table 3
Micrometric properties and packing or flow parameters of spherical crystal agglomerates prepared under different supersaturation ratios

Ibuprofen:Eudragit® ratio	Particle size		Particle shape		Density (g/ml)		Packing parameters	
	d_g (μm)	σ_g	Roundness	D_f	Bulk	Tapped	CI (%)	Angle of repose (θ°)
80/0	1150	1.53	7.9	1.07	0.39	0.45	13.2	58
35/3.5	2010	1.83	2.3	1.13	0.37	0.39	5.9	34
50/5.0	1900	2.02	2.4	1.13	0.35	0.40	10.6	34
65/6.5	1160	2.15	3.4	1.20	0.27	0.31	11.1	45
80/8	975	2.07	7.6	1.22	0.27	0.31	11.9	44
65/8	1910	2.03	4.4	1.26	0.26	0.28	8.1	41
50/8	2000	1.54	2.8	1.26	0.36	0.39	7.9	34
35/8	1110	1.24	2.7	1.19	0.32	0.35	5.4	34

standard deviation (σ_g) change (Table 3). The value of σ_g changes inversely to d_g and for all the spherical agglomerates containing Eudragit it is greater than that of the reference sample, except for the drug:polymer ratio 35/8. High values of σ_g represent a wider size distribution and the presence of large and small agglomerates in a greater proportion. All these particle size changes of the agglomerates can be attributed to possible alterations in crystal habit of ibuprofen microcrystals (Labhasetwar et al., 1993).

Regarding the effects of stirring and cooling rate on size, the results in Table 4 show that d_g assumes a maximum value with the intermediate cooling rate (0.33°C/min) and low stirring rate (300 rpm), but with the slow cooling rate (0.22°C/min) at higher stirring rates (600 and 900 rpm). Also, the results in Table 4 show that stirring exerts no significant effect on the value of d_g in the case of the high cooling rate (0.66°C/min), but in the case of intermediate cooling rate (0.33°C/min) d_g decreases with stirring, while in the case of slow cooling (0.22°C/min) it increases.

Table 4
Micrometric properties and packing or flow parameters of spherical agglomerates prepared at a constant ibuprofen:Eudragit® ratio (80/8) employing different cooling and stirring rates

Stirring rate (rpm)	Cooling rate [a] (°C/min)	Particle size		Particle shape		Density (g/ml)		Flow parameters	
		d_g (μm)	σ_g	Roundness	D_f	Bulk	Tapped	CI (%)	Angle of repose (θ°)
300	0.22	975	2.27	11.0	1.16	0.25	0.29	16.3	56
600		1250	2.00	4.9	1.14	0.26	0.31	13.6	44
900		1400	1.93	3.5	1.13	0.33	0.37	11.2	39
300	0.33	1350	1.86	4.4	1.17	0.21	0.25	16.6	48
600		975	2.07	7.6	1.22	0.27	0.31	11.9	44
900		750	1.79	2.5	1.10	0.34	0.39	12.9	39
300	0.66	970	2.31	2.5	1.12	0.21	0.23	10.7	48
600		1100	2.16	2.8	1.20	0.21	0.25	15.1	49
900		950	2.32	3.2	1.14	0.20	0.23	15.9	45

[a] Cooling rates of 0.22, 0.33 and 0.66°C/min correspond to water addition rates of 3.9, 5.8 and 11.6 ml/min, respectively.

Table 5
Density, porosity and parameters of Heckel's compression equation for spherical crystal agglomerates prepared under different supersaturation ratios

Ibuprofen:Eudragit® ratio (g/g)	Density (g/ml)		Porosity (%)				Pore mean diameter (μm)	Heckel's equation parameters	
	True	Particle	ϵ_{inter}	ϵ_{intra}	ϵ_{12-40}	$\epsilon_{<12}$		D_B	P_y (MPa, mean ± S.D.)
80/0.0	1.076	0.733	51.9	31.9	21.7	10.2	16.0	0.41	20.2 ± 3.1
35/3.5	1.098	0.705	44.7	35.8	22.7	13.1	13.0	0.36	36.3 ± 6.9
50/5.0	1.089	0.713	43.9	34.5	21.2	13.3	13.0	0.39	34.6 ± 7.4
65/6.5	1.091	0.623	50.2	42.9	29.3	13.6	19.0	0.51	37.0 ± 8.7
80/8.0	1.085	0.618	49.8	44.1	29.8	14.3	18.0	0.50	30.6 ± 4.8
65/8.0	1.106	0.632	55.7	42.8	26.9	15.9	18.5	0.51	47.3 ± 10.4
50/8.0	1.109	0.729	46.5	34.3	20.0	14.3	17.0	0.37	54.1 ± 6.4
35/8.0	1.116	0.791	55.7	29.1	17.5	11.6	18.0	0.37	49.7 ± 9.6

Applying 3^2 factorial analysis to the particle size results it was found that neither cooling nor stirring, nor their combination, exert a statistically significant effect on particle size. However, a possible explanation for the complex d_g changes with cooling and stirring can be based on the combined effect of polymer solidification and microcrystal collisions. Polymer solidification affects mainly the binding of microcrystals into agglomerates, while stirring rate affects mainly the microcrystal development, the growth, the collisions and therefore the agglomeration. In other words, fast cooling should result in quick solidification of the polymer and consequently minimisation of the stirring rate effect on the values of d_g and σ_g of agglomerates. As the cooling rate is reduced, stirring exerts a greater effect on crystal growth; this is confirmed from the mean 'apparent crystal growth' rate changes due to stirring (Table 2). Therefore, at intermediate cooling more small-sized crystals are formed, which should be responsible for the d_g decrease with stirring rate. Finally,

Table 6
Density, porosity and parameters of Heckel's compression equation for spherical crystal agglomerates prepared at a constant ibuprofen:Eudragit® ratio (80/8) employing different cooling and stirring rates

Stirring rate (rpm)	Cooling rate [a] (°C/min)	Density (g/ml)		Porosity (ε%)				Pore mean diameter (μm)	Heckel equation parameters	
		True	Particle	ϵ_{inter}	ϵ_{intra}	ϵ_{12-40}	$\epsilon_{<12}$		D_B	P_y (MPa, mean ± S.D.)
300	0.22	1.082	0.758	59.1	30.0	25.7	4.3	20.5	0.53	30.4 ± 7.3
600		1.080	0.637	54.5	41.0	30.4	10.6	20.0	0.47	28.1 ± 2.6
900		1.079	0.723	48.8	33.0	19.3	13.7	15.0	0.45	30.2 ± 3.5
300	0.33	1.079	0.763	67.2	29.3	25.6	3.7	19.0	0.53	27.2 ± 5.6
600		1.080	0.618	49.8	44.1	29.8	14.3	18.0	0.49	30.6 ± 4.8
900		1.080	0.781	50.1	27.7	20.4	7.3	20.0	0.42	29.3 ± 5.1
300	0.66	1.081	0.741	69.0	31.4	29.0	2.4	16.0	0.52	31.4 ± 6.0
600		1.080	0.577	56.7	46.6	35.4	11.2	21.0	0.61	46.3 ± 5.3
900		1.081	0.450	48.9	58.4	37.2	21.2	19.0	0.57	43.8 ± 8.8

[a] Cooling rates of 0.22, 0.33 and 0.66°C/min correspond to water addition rates of 3.9, 5.8 and 11.6 ml/min, respectively.

in the case of slow cooling (0.22°C/min), the increase in the value of d_g with stirring can be attributed to the combination of longer polymer solidification and of increased frequency and intensity of the collisions between microcrystals at higher stirring. They both, combined with the increased growth rate, result in the formation of larger and more spherical agglomerates.

3.5.2. Shape

The particle shape results (Table 3) show that roundness of all the spherical agglomerates prepared in the presence of polymer is lower and the value of the fractal dimension (D_f) greater, in comparison to those of the reference sample. In other words, it seems that the presence of polymer contributes to improved sphericity and increased surface roughness of the agglomerates. Improvement of sphericity may be attributed to a coating developed on the microcrystals before their binding into agglomerates, which can result in improved symmetry of packing and therefore sphericity. Surface roughness increase may be attributed to habit change of the microcrystals developed. Scanning electron photomicrographs (Fig. 3a,b) show a looser structure of acircular microcrystals for the reference sample (Fig. 3a) and closer packing of tabular microcrystals in the case of agglomerates prepared in presence of polymer (Fig. 3b).

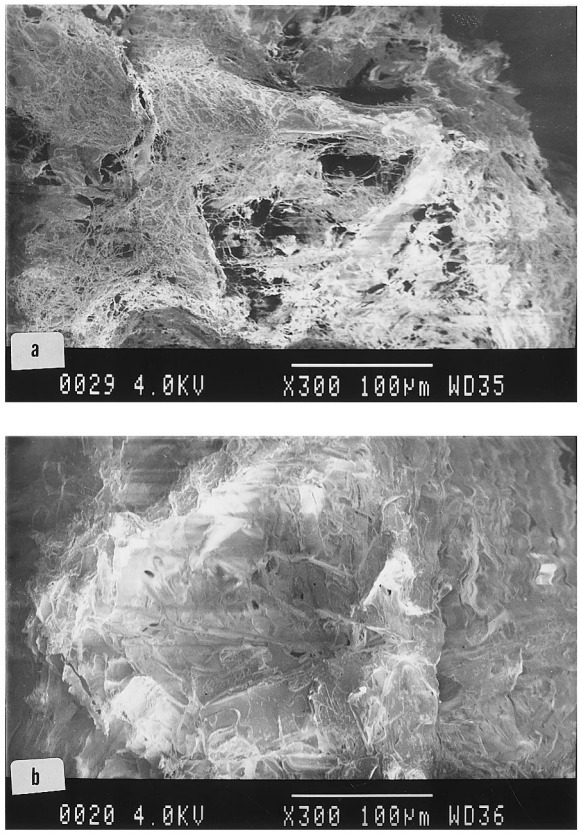

Fig. 3. Scanning electron photomicrographs of spherical crystal agglomerates: (a) reference sample, (b) agglomerates of Ibuprofen:Eudragit® 80/8 g, 600 rpm, 0.33°C/min cooling rate.

As far as the stirring and cooling effect on sphericity and surface roughness of agglomerates is concerned, the results in Table 4 show that the fractal dimension (D_f) does not differ significantly and the greatest improvement of sphericity corresponds to high stirring and low cooling rate. The last is confirmed by the scanning electron photomicrographs (Fig. $4a_1$–b_2). Also, the results in Table 4 indicate that the surface roughness expressed as D_f does not change in parallel with sphericity due to alteration of stirring and cooling applied. Therefore, we can suppose that surface roughness depends on the habit of ibuprofen microcrystals constituting the agglomerates. Regarding the stirring effect alone, we can say that it alters with cooling. In the case of slow cooling, sphericity increases with stirring, while in the case of fast cooling it decreases. In the case of intermediate cooling rate, 0.33°C/min, the effect of stirring does not seem to be significant.

The above changes of sphericity due to stirring and cooling can be attributed to two factors which are considered responsible for the size changes as well: (1) the polymer's binding ability, which is determined by the cooling rate; (2) the attachment and detachment of microcrystals in agglomerates, which is determined by the intensity and the frequency of the collisions between microcrystals or by the speed and duration of stirring. In other words, sphericity may increase either due to closer and/or symmetrical packing of microcrystals under shear caused by stirring or due to extensive detachment of small fragments from the surface and smoothing of particle edges. Since the effect of stirring on sphericity is less predominant with fast cooling, the improvement of sphericity

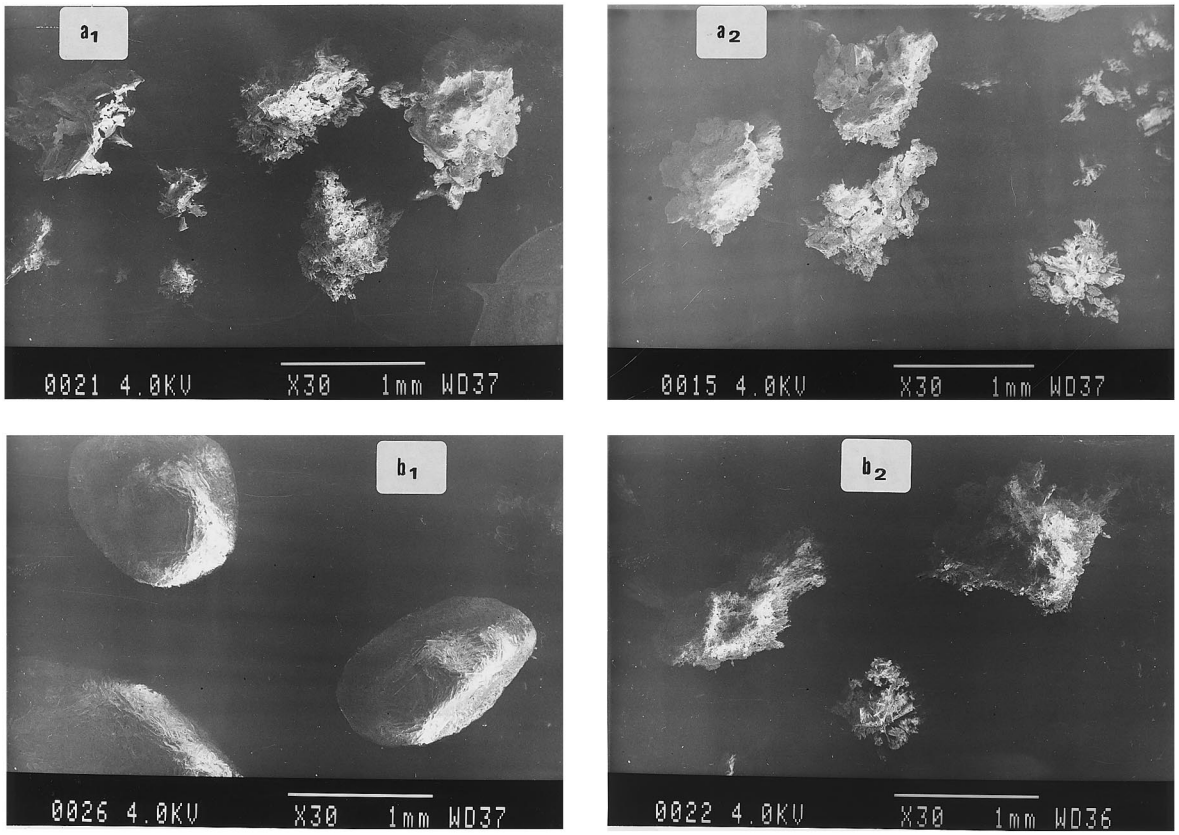

Fig. 4. Scanning electron photomicrographs of spherical crystal agglomerates prepared under different stirring and cooling rates: (a) 300 rpm, (b) 900 rpm, (1) 0.22°C/min, (2) 0.66°C/min.

with slow cooling (0.22°C/min) or prolonged and fast stirring observed (Fig. 4b_1) could be attributed to detachment of small fragments from their surface and smoothing of edges.

3.5.3. Packing and flow parameters

The bulk and tapped density of all the spherical crystal agglomerates prepared in the presence of Eudragit® (Table 3) are lower than those of the reference sample, although their particle size and sphericity, in general, are higher. Therefore, these reductions should be related to the intraparticle porosity or particle density (Table 5). As far as CI and angle of repose are concerned (Table 3), it is seen that both increase with the amount of ibuprofen added initially in the crystallisation liquid when the drug:polymer ratio is kept constant and, furthermore, they decrease with the presence of polymer. These decreases indicate improvement in flow and packing ability of agglomerates that can be attributed to improvement of sphericity.

Applying 3^2-factorial analysis, it was found that changes in CI (Table 4) are significant only due to a combination of stirring and cooling (0.1 level), while those of angle of repose are significant due to stirring (0.01 level) and due to a combination of stirring and cooling (0.05 level). Also, the results in Table 4 show that bulk and tapped density in general decrease with cooling rate, while they increase with stirring rate, especially at low cooling rate. These changes of bulk and tapped density should be related to size, shape and mainly to surface roughness of the agglomerates. Smaller, less spherical and rougher agglomerates contribute to looser packing and smaller bulk and tapped density due to greater interparticle contact area and friction.

3.5.4. Density and porosity

True density for all the agglomerates prepared in the presence of polymer is higher, while their particle density shows positive and negative deviations (less than 10%) from that of the reference sample (Table 5). The increase in true density is probably due to the higher true density of Eudragit® (1.450) than that of ibuprofen (1.076), while the particle density changes seem to depend on the intraparticle porosity (Table 5).

Total intraparticle porosity (ϵ_{intra}), given in Table 5, is always higher, while interparticle porosity shows positive and negative deviations from that of the reference sample, such as particle density (range $\pm$ 10%). The increase in intraparticle porosity corresponds to pores with diameter smaller than 12 μm ($\epsilon_{<12}$), since the fraction of intraparticle pores with diameter between 12 and 40 μm (ϵ_{12-40}) shows positive and negative deviation (range $\pm$ 30%) compared to that of the reference sample. Also, both ϵ_{intra} and $\epsilon_{<12}$ seem to increase with initial supersaturation. As far as pore mean diameter is concerned, it is larger than that of the reference sample in all the cases of agglomerates, except for those with drug:polymer ratios of 35/3.5 and 50/5.

The increase of pore diameter in combination with the increase in the fraction of intraparticle pores with diameter less than 12 μm ($\epsilon_{<12}$), observed due to polymer presence, indicate the absence of polymer deposition in empty spaces between microcrystals. Therefore, they should be attributed to coating and habit change of ibuprofen microcrystals comprising the agglomerates. Coating is probably developed before binding into spherical agglomerates leading to greater resistance to rearrangement and looser packing due to collisions.

The changes of density and porosity due to stirring and cooling rate alteration, given in Table 6, show that: (1) the true density is unaffected, as expected; (2) the interparticle porosity decreases with stirring in all the cases of cooling rates employed; (3) the total intraparticle porosity (ϵ_{intra}) and the fractions ϵ_{12-40} and $\epsilon_{<12}$ increase with stirring in the case of fast cooling (0.66°C/min), while in the cases of intermediate and slow cooling rates they assume maximum value under different stirring rates.

The decrease in interparticle porosity with stirring may be attributed to closer packing of agglomerates due to improved sphericity. But the complex changes of intraparticle porosity with cooling and stirring could be caused from the alterations in packing of coated microcrystals during their binding into agglomerates due to the change of habit and size or growth rate.

3.5.5. Compression behaviour

The compression behaviour of the spherical agglomerates is expressed as parameters of the Heckel equation (Heckel, 1961), namely the relative density (D_B) and the yield pressure (P_y) presented in Table 5. Also, representative Heckel plots are given in Fig. 5. D_B describes the extent of increase in packing at the early stages of compression. It has been obtained from the difference between the packing fraction corresponding to the intercept of the extrapolated linear part of Heckel plots (Fig. 5) and the value corresponding to the tapped density of agglomerates. The yield pressure (P_y) is the reciprocal of the slope in the linear part of the Heckel plot.

From the results in Table 5 it is seen that D_B increases with the initial supersaturation ratio and is lower than that of the reference sample in the

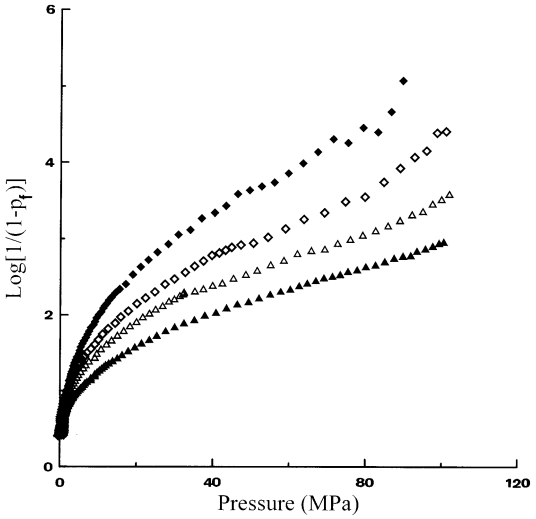

Fig. 5. Heckel plots for spherical crystal agglomerates prepared with different ibuprofen:Eudragit® ratios: ▲, 35/8; △, 35/3.5; ◇ 80/8; ◆80/0 (reference sample).

cases of the ibuprofen:Eudragit® ratios 35/3.5 and 50/5, but higher in the case of 65/6.5, 80/8 and 35/8 ratios. The yield pressure for all the batches prepared in the presence of Eudragit® is higher than that of the reference sample.

The results of Table 6 show the effect of stirring and cooling rate on the Heckel parameters (D_B and P_y). D_B seems to decrease with stirring, but only for the cases of slow and intermediate cooling. Comparing the D_B (Tables 5 and 6) and the particle properties (Tables 3 and 4), the D_B changes should be attributed to easier movement of the agglomerates due to size change and mainly due to improvement of sphericity caused by the presence of polymer. Furthermore, the presence of polymer should be responsible for the increase of yield pressure observed in comparison to that of the reference sample. Eudragit® S100, with a brittle fracture index (BFI) of 1.20 (Schulze and McGinity, 1993), is less plastic and more brittle than ibuprofen with a BFI value of 0.06 (Hiestand, 1996). Therefore, the increase of fragmentation of spherical crystal agglomerates should result in the yield pressure increase observed.

The yield pressure (P_y) results (Table 6) do not change significantly with stirring and cooling rate, as is expected, since yield pressure is determined by the polymer content of the spherical agglomerates and it remains unchanged in all the batches prepared under different stirring and cooling rate.

4. Conclusions

From the above it can be concluded that when spherical crystallisation of ibuprofen is applied in presence of Eudragit® S100 with ethanol and water as miscible solvents:

(1) Crystal yield and drug loading efficiency are not affected by the crystallisation conditions, while the mean 'apparent crystal growth' rate increases with the initial supersaturation ratio and the stirring rate, but the cooling effect is stirring dependent, probably due to a change in the nucleation mechanism.

(2) Particle size decreases while sphericity, surface roughness and intraparticle porosity increase with polymer presence, probably due to changes in habit and growth rate of ibuprofen microcrystals, as well as to a coating developed before their binding into spherical agglomerates. In addition, particle size and sphericity decrease while intraparticle porosity increases with initial supersaturation.

(3) Slow cooling enhances the stirring rate effect on particle size and sphericity becomes maximal with slow cooling and fast stirring. These size and sphericity changes are attributed to the polymer binding ability determined by its solidification or the cooling rate applied and to the detachment of small fragments from the surface determined by the stirring rate.

(4) Flow or packing behaviour and densification of agglomerates at low compression are determined by the sphericity changes, while yield pressure is determined by the brittleness due to the polymer incorporated.

Acknowledgements

K.K. thanks the Greek State Scholarships Foundation for the award of a scholarship.

References

Akbuga, J., 1989. Preparation and evaluation of controlled release furosemide microspheres by spherical crystallisation. Int. J. Pharm. 53, 99–105.

Arica, B., Arica, M.Y., Kas, H.S., Hincal, A.A., Hasirci, V., 1996. In-vitro studies of enteric coated diclofenac sodium-carboxymethylcellulose microspheres. J. Microencapsulation 13, 689–699.

Beten, D.B., Gelbcke, M., Diallo, B., Moës, A.J., 1992. Interaction between dipyridamole and Eudragit® S. Int. J. Pharm. 88, 31–37.

Carr, R.L., 1965. Evaluating flow properties of solids. Chem. Eng. 18, 163–168.

Dew, M.J., Hughes, P.J., Lee, M.G., Evans, B.K., Rhodes, J., 1982. An oral preparation to release drugs in the human colon. Br. J. Clin. Pharmacol. 14, 405–408.

Flook, A.G., 1978. The use of dilation logic on the Quantimet to achieve fractal dimension characterisation of textured and structured profiles. Powder Technol. 21, 295–298.

Ford, G.A., Oliver, P.S., Shepherd, N.A., Wilkinson, S.P., 1992. An Eudragit®-coated prednisolone preparation for ulcerative colitis: pharmacokinetics and preliminary therapeutic use. Aliment. Pharmacol. Ther. 6, 31–40.

Goto, S., Kawata, M., Nakamura, M., Nagatsumma, Y., Fujinaga, K., Aoyama, T., 1988. Evaluation of the sustained release properties of Eudragit® RS, RL and S (acrylic resins) microcapsules containing ketoprofen in beagle dogs. J. Microencapsulation 5, 343–360.

Heckel, R.W., 1961. An analysis of powder compaction phenomena. Trans. Metall. Soc. AIME 221, 671–675.

Hiestand, E.N., 1996. Rationale for and measurement of powder compaction technology. In: Alderborn, G., Nyström, C. (Eds.), Pharmaceutical Powder Compaction Technology, Marcel Dekker, New York, p. 243.

Kawashima, Y., Okumura, M., Takenaka, H., 1982. Spherical crystallisation: direct spherical agglomeration of salicylic acid crystals during crystallisation. Science 216, 1127–1128.

Kawashima, Y., Niwa, T., Handa, T., Takeuchi, H., Iwamoto, T., Itoh, K., 1989. Preparation of controlled-release microspheres of ibuprofen with acrylic polymers by a novel quasi-emulsion solvent diffusion method. J. Pharm. Sci. 78, 68–72.

Khan, M.A., Bolton, S., Kislalioglou, M.S., 1994. Optimization of process variables for the preparation of ibuprofen coprecipitates with Eudragit® S100. Int. J. Pharm. 102, 185–192.

Kislalioglou, M.S., Khan, M.A., Blount, C., Goettsch, R.W., Bolton, S., 1991. Physical characterization and dissolution properties of ibuprofen:Eudragit® coprecipitates. J. Pharm. Sci. 80, 799–804.

Labhasetwar, V., Deshmuck, S.V., Dorle, A.K., 1993. Studies on some crystalline forms of ibuprofen. Drug Dev. Ind. Pharm. 19, 631–641.

Marshall, P.V., York, P., Richardson, R., 1986. The effect of compression on the axial recovery properties of compacts of a crystalline drug substance. J. Pharm. Pharmacol. 38, 47P.

Mullin, J.W., 1993. Crystallisation, 3rd ed. Butterworth-Heinemann, Oxford, pp. 180–181.

Pilpel, N., 1964. The flow properties of magnesia. J. Pharm. Pharmacol. 16, 705–716.

Schulze, M.D., McGinity, J.W., 1993. Indices of tabletting performance for acrylic resin polymers with plastic and brittle drugs. Drug Dev. Ind. Pharm. 19, 1393–1411.

Strickland, W.A. Jr., Busse, L.W., Higuchi, T., 1956. The physics of tablet compression XI. Determination of porosity of tablet granulations. J. Am. Pharm. Assoc. 45, 482–486.