Spherical Crystal Agglomeration of Ibuprofen by the Solvent-Change Technique in Presence of Methacrylic Polymers

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ABSTRACT: The effects of Eudragit® nature on the formation and spherical agglomeration of ibuprofen microcrystals have been examined when solvent change (ethanol-water) technique is applied. Four methacrylic polymers (Eudragit® S100, L100, RS, and RL), with different solubility and solubilizing ability, were used. The extrapolated points of maximum temperature deviation rate in crystallization liquid that reflect the maximum crystallization rate and the corresponding water addition were determined, as well as crystal yielding and incorporation of drug and polymer in the agglomerates. The physicomechanical properties of the agglomerates, such as size, sphericity, surface roughness and porosity, as well as flow and packing or compression behavior during tableting, were evaluated for different drug/polymer ratios. It was found that crystal yield is greatly reduced in the presence of water-insoluble polymers and that formation of the microcrystals and incorporation of drug and polymer are affected by the polymer nature. Crystal formation changes are attributed to alterations in the metastable zone, whereas the changes in drug and polymer incorporation and crystal yield are caused by changes in the polymers' solubility and micellization. The size of agglomerates depends on the polymer nature and its interactions with the ibuprofen microcrystals formed. Sphericity, surface roughness, and intraparticle porosity of agglomerates increase, in general, with the presence of polymer owing to changes in habit and growth rate of the microcrystals and to their coating before binding into spherical agglomerates. The particle density or intraparticle porosity and size changes determine flow or packing behavior and densification of agglomerates at low compression. The incorporation and brittleness of the polymer determine the deformation under higher compression pressure, expressed as yield pressure, Py. © 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 89: 250–259, 2000

INTRODUCTION

Ibuprofen [2-(4-isobutylphenyl)propionic acid] is a nonsteroidal anti-inflammatory drug that is used in high doses (200–800 mg every 4–6 hours). The danger for occurrence of adverse effects after oral delivery of ibuprofen is significant because of its specific biologic characteristics (rapid absorption, high [more than 80 %] bioavailability, and short [2.0 ± 0.5 hours] biologic half-life).[1] Therefore, interest in sustained, or enteric-release, oral dosage forms of ibuprofen is justified.

Methacrylic copolymers (Eudragit®) are offered in a variety of types with different water solubility and permeability properties and have been used for drug release modification in several oral solid dosage forms.[2–5] Eudragit® S100 and L100 have pH-dependent solubility in water, whereas Eudragit® RS and RL are insoluble but water permeable. Because Eudragit® L100 is soluble at pH > 6 and S100 at pH > 7, both are used as enteric

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coating materials resistant to the gastric fluid.[6] Eudragit® RS is slightly water permeable, whereas RL is freely permeable to water because of higher content of quaternary ammonium groups. Both Eudragit® RS and RL, therefore, are used for the production of sustained-release formulations.[7] For the enteric release of ibuprofen the preparation of spherical crystal agglomerates with Eudragit® S100 has been suggested by applying the solvent change technique, and recently the effects of crystallization conditions on their physicomechanical properties have been investigated.[8–10] It was found that the fundamental agglomerate properties are affected by changes in the habit and growth of ibuprofen crystals caused by the presence of polymer.[10]

Spherical crystallization was defined as an agglomeration technique that directly transforms crystals into a compacted spherical form during the crystallization process.[11] Until now two main variations of this technique have been applied: the spherical agglomeration (SA) and the quasi-emulsion solvent diffusion (QESD). Modifications have been suggested for specific drug formulation purposes.[12,13] Because habit of microcrystals and their growth and agglomeration may be affected by the conditions of spherical crystallization, as well as by the presence of polymer added as a binder, it was of interest to examine the effects of Eudragit® on the formation and agglomeration of ibuprofen microcrystals.

In this study we compare the crystallization parameters and the physicomechanical properties of spherical crystal agglomerates when the solvent change (ethanol-water) technique is applied in the presence of methacrylic (Eudragit®) polymers of different solubility and solubilizing ability.

EXPERIMENTAL SECTION

Materials

Crystalline ibuprofen (USP grade, from Boots Pharmaceuticals, Nottingham, England, supplied by Vianex, Athens, Greece) and four methacrylic copolymers in powder form (Eudragit® S100, L100, RS, and RL, supplied by Röhm Pharma, Darmstadt, Germany) were used as main constituents. Water distilled by an all-glass apparatus and analytical grade absolute ethanol (Merck, Darmstadt, Germany) were used as poor and good solvent, respectively. Mercury (Merck, Darmstadt, Germany) was used as the displacement liquid for the porosity determination. Because Eudragit® S100 and L100 have pH-dependent solubility, the pH of the distilled water was measured and was found to be 5.96 ± 0.01.

Preparation of Spherical Crystal Agglomerates

Sixteen batches of spherical crystal agglomerates were obtained by using each type of polymer at four drug/polymer ratios: 35 : 8, 50 : 8, 65 : 8, and 80 : 8 g and one batch by using 80 g of ibuprofen in the absence of polymer (reference sample). The amounts of ibuprofen, ethanol, and water used were selected for maximal yield of agglomerates, after determination of ibuprofen solubility in different mixtures of water and 8% w/w ethanolic polymer solution, at the mean crystallization temperature (30°C, Fig. 1).

For the determination of ibuprofen solubility in the presence of the polymers, excess ibuprofen powder was dispersed in the mixtures of water and ethanolic polymer solutions. After shaking for 72 hours at 30°C, aliquots of the supernatant solution were filtered by positive pressure. The filtrates, after appropriate dilution, were assayed spectrophotometrically. These results, Figure 1, show the solubilizing ability of polymers and may allow elucidation of the effect of their presence on

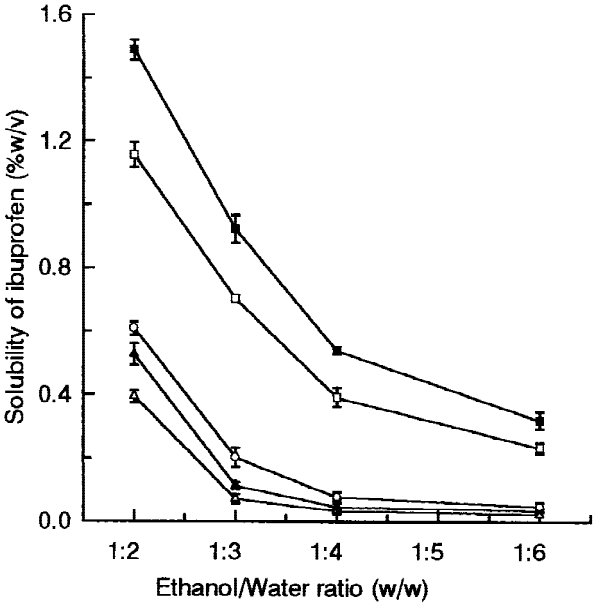

Figure 1. Solubility of ibuprofen in different mixtures of water and 8% w/w ethanolic polymer solutions, at 30°C: ▲, S100; △, L100; ■, RS; □, RL; and ○, reference sample.

the supersaturation of the crystallization medium as well.

For the preparation of spherical crystal agglomerates, an apparatus described previously was used.[10] The applied procedure was as follows: Specified amounts of crystalline ibuprofen (35–80 g) and 8.0 g of polymer were dissolved in 100 g of ethanol, kept under constant agitation (600 rpm) and temperature (50°C), inside a 1000-ml (7 × 30 cm) crystallization vessel. Subsequently, distilled water (700 ml) was added at a constant rate (5.9 ml/min), whereas cooling was applied from 50°C down to 10°C with a programmable refrigerated circulator (0.33°C/min). The temperature of the crystallization liquid was recorded, and extrapolated points of maximum temperature deviation rate were determined together with the corresponding water consumption as parameters of maximum crystallization rate.

The agglomerates produced were collected by vacuum filtration, dried at 50°C in a vacuum oven, and kept in screw-capped, amber glass jars. Crystal yield was calculated from the weight of agglomerates and their drug content. The variation of drug content in five sieve-fractions of different size was determined as well. In addition, the physicomechanical properties that may affect the quality of tablets and capsules produced from spherical crystal agglomerates, such as the micromeritic properties (size and size distribution, shape, surface roughness, density, and porosity), the flow or packing, and the compression behavior were assessed.

Characterization of Spherical Crystal Agglomerates

Size was evaluated as geometric mean diameter (d_g) and size distribution as geometric standard deviation (σ_g). These values were determined by sieve analysis, after plotting cumulative undersize weight percentage on a log-probability scale versus sieve size on a logarithmic scale. The size corresponding to 50% cumulative undersize is d_g, and σ_g is the size ratio of 84.13 : 50% undersize. Shape and surface roughness were quantified as roundness and fractal dimension (D_f), respectively, by using an image processing and analysis system (Quantimet 500, Leica, Cambridge, England). Roundness is the square of perimeter divided by 12.56 times the projection area and assumes a value of 1 for a sphere. Fractal dimension (D_f) was determined with a successive dilation sequence from the slope of logarithmic plots of perimeter length versus measuring unit ("Richardson" plots) as: $D_f = 1 + |\text{slope}|$.[14] In addition, scanning electron photomicrographs were taken to see the morphology and structure of the agglomerates. Density was determined as true, loose bulk and tapped density. Porosity was measured using the pyknometric method of Strickland.[15] Intrusion pressures between 360 and 1200 mm Hg were applied, which correspond to a pore diameter range of about 40 to 12 μm. The following parameters were calculated: the particle density; the interparticle and intraparticle porosity; the fraction of pores with diameter 40 to 12 μm and <12 μm; and the mean pore diameter.

The flow behavior was quantified as compressibility index (C.I. %) and angle of repose. The compression behavior was expressed as parameters in Heckel's equation (densification at low pressure, D_B, and yield pressure, P_y) determined with an instrumented single punch tableting machine. All the equipment and methods used for the characterization of spherical crystal agglomerates have been described previously.[10]

RESULTS AND DISCUSSION

Crystallization Parameters

The crystal yield results given in Table I show significant alterations caused by changes either in the nature of polymer added or in the drug/polymer ratio applied. Small reductions in crystal yield (<10%), similar to that of the reference sample, correspond to the cases of water-soluble polymers (S100 and L100), which reduce the ibuprofen solubility in ethanol/water mixtures (Fig. 1). On the contrary, in the cases of water-insoluble polymers (RS and RL) that increase the ibuprofen solubility in ethanol/water mixtures, there is a significant reduction in crystal yield, particularly at the lower drug/polymer ratios.

Solubilization of ibuprofen by Eudragit® RS and RL, shown in Figure 1, can be attributed to electrostatic interactions with the quaternary ammonium groups existing in their molecules, already reported for other acidic pharmaceutical compounds.[16]

The amounts of ibuprofen and polymer lost in the crystallization liquid were calculated from the weight of agglomerates produced and their drug content (Table I). These losses are small and almost independent of the amount of drug added initially (supersaturation ratio), when the water-soluble polymers (S100 and L100), which decrease the solubility of ibuprofen (Fig. 1), are

Table I. Crystallization Parameters for Ibuprofen Spherical Crystal Agglomerates Prepared with Different Eudragit® and Increasing Drug/Polymer Ratio

Eudragit Type and Drug/Polymer Ratio (g/g)		Crystal Yield (%)	Drug Content (% w/w) ±(CV%)[a]	Drug Lost (g)	Polymer Lost (g)	Point of Maximum Temperature Deviation Rate (°C)	Water Consumption (ml)
	80/0	94.3	100 (1.1)	4.6	0.0	36.1	290
S100	35/8	90.5	84.0 (0.1)	2.3	1.8	33.8	296
	50/8	92.8	88.3 (0.3)	2.5	1.7	32.6	304
	65/8	95.9	91.5 (0.9)	2.0	1.8	35.6	290
	80/8	95.2	93.0 (3.4)	2.1	2.1	35.6	292
L100	35/8	91.2	85.0 (3.0)	1.7	2.1	32.0	312
	50/8	95.2	89.0 (1.9)	1.9	1.9	36.7 (32.0)[b]	272
	65/8	95.5	90.0 (0.7)	2.3	1.0	38.6 (36.3)[b]	245
	80/8	91.8	91.0 (1.4)	2.5	0.7	39.5 (37.2)[b]	228
RS	35/8	43.3	91.0 (1.1)	12.7	5.8	31.7	320
	50/8	57.0	92.0 (1.1)	26.9	6.0	31.7	320
	65/8	88.9	93.0 (0.7)	4.6	3.5	35.1	316
	80/8	91.9	95.5 (1.0)	2.7	4.4	34.9	285
RL	35/8	64.2	98.0 (3.5)	7.9	7.4	31.7	350
	50/8	78.0	98.0 (0.8)	5.7	7.1	31.7	350
	65/8	80.1	96.5 (0.7)	8.5	5.9	30.8	332
	80/8	87.5	96.0 (1.7)	6.1	4.9	33.3	320

[a] CV% = coefficient of variation for drug content in five sieve fractions.
[b] Second extrapolated onset of temperature deviation.

added. On the contrary, losses increase and are inversely related to the amount of drug added, with the water-insoluble polymers (RS and RL), which enhance drug solubility (Fig. 1). The distribution of the constituents (drug and polymer) is independent of the agglomerates' size because the coefficient of drug content variation, C.V. %, between the sieve-fractions was found to be less than 3.5% (Table I). Therefore, the reduction in the crystal yield must be caused by the relative losses of polymer and ibuprofen.

Massive crystal formation is completed long before the end of cooling or water addition, as is evident from the temperature plots (Fig. 2). Also, the increase of ibuprofen solubility in the presence of RS and RL (Fig. 1) cannot explain the great extent of yield reduction observed. Therefore, the most probable explanation is colloidal dispersion of both ibuprofen and polymer in the crystallization medium in addition to the dissolution.

Opacity of the crystallization liquid was observed after the collection of the agglomerates by filtration for the cases of water-insoluble Eudragit® RS and RL at low drug/polymer ratios (35 : 8 and 50 : 8). Therefore, reduction of polymer solubility caused by the water addition and excess of critical micelle concentration (CMC) may lead to formation of micelles of Eudragit® RS and RL polymers because of the existence of quaternary ammonium groups in their molecules. Subse-

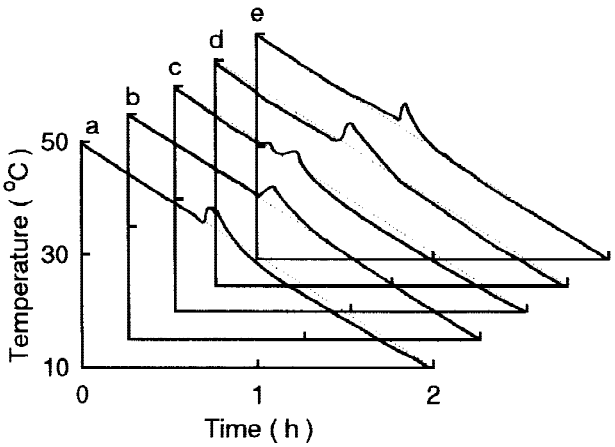

Figure 2. Typical temperature versus time plots of the crystallization liquid corresponding to different Eudragit® polymers, at drug/polymer ratio 80/8 g (polymer: a, none (reference sample); b, S100; c, L100; d, RS; and e, RL).

quent engulfing of ibuprofen by the micelles could be the reason for the great increase in drug loss, particularly in the case of Eudragit® RS. The amount of water required for the separation of the polymers from solution (appearance of permanent turbidity) and the temperature at which this occurred in the absence of ibuprofen (blank solution) were determined and the results are presented in Table II. It is seen that the amount of water is reduced in the order L100 > S100 > RL > RS, or for the less water-soluble polymers turbidity appears at higher temperature and smaller amount of water as expected.

Figure 2 shows typical temperature versus time plots for the crystallization liquid of different polymers at a certain drug/polymer ratio (80 : 8 g). Straight dotted lines correspond to the programmed temperature and the positive deviation is due to heat released during crystallization of ibuprofen. Onset and endset points should indicate initiation and cessation of massive crystallization, respectively, whereas the point of maximum temperature deviation rate corresponds to maximum crystal growth rate (i.e., to maximum supersaturation ratio). For the case of Eudragit® L100, two maxima of temperature deviation appear at two different combinations of temperature and water consumption. This can be attributed to great enhancement in the formation of ibuprofen microcrystals. In other words, faster release of latent heat of crystallization and quick increase in the temperature of the crystallization liquid causes an increase in the solubility of ibuprofen, thus slowing down the formation and growth of crystals at this low water addition level. Subsequently, when the reduction of ibuprofen solubility caused by water addition is smaller (Fig. 1) and the released latent heat of crystallization is controlled by the cooling system, the rate of crystal formation increases again and attains a second (final) maximum because of reduction in the amount of ibuprofen.

Two maxima of temperature deviation, as seen with L100, might also be expected for the case of Eudragit® S100 because it also reduces the solubility of ibuprofen. However, a single maximum is observed instead. The reason for this difference may lie either in the lower solubility of S100 resulting in a greater amount of solvent being available to interact with ibuprofen at the crystallization point or in less hydrogen bonding between carboxylic groups of polymer and drug. Compared with S100, L100 contains twice the amount of free carboxyl groups, which are hydrogen bond donors and acceptors as well.

The area under the curve (AUC) of the temperature deviation plots (Fig. 2) did not indicate any change in crystal formation caused by the presence of polymer. This is because in addition to the level at which temperature deviation occurs, the AUC is also affected by the cooling capacity of the system used. Therefore, the AUC results show only the expected increase caused by the amount of ibuprofen added in the crystallization solution (initial supersaturation). Furthermore, the initial supersaturation affects the point of maximum rate in temperature deviation and the water consumption. The alteration in the formation of the crystals caused by the presence of the polymer is evident from the extrapolated point of maximum temperature deviation rate and from the corresponding water consumption (Table I) when certain amounts of ibuprofen and polymer are added (80 : 8 g). This point, in the case of the reference sample, is higher, and the corresponding water consumption is lower compared with those for the samples prepared in presence of polymer, except in the case of Eudragit® L100. Furthermore, the changes of the extrapolated point of maximum temperature deviation rate and of corresponding water consumption for the different polymers used are in parallel to those of the alteration in the solubility of ibuprofen (Fig. 1).

Considering that initiation of crystallization occurs when the supersaturation ratio reaches a critical value because of cooling and water addition, all the aforementioned alterations in crystallization parameters confirm that this value is determined by both the amount of ibuprofen and the nature of polymer (type of Eudragit®). In other words, they indicate that the type of Eudragit® affects the solubility of ibuprofen and the supersaturation ratio or the width of the metastable zone.[17]

Table II. Temperature and Water Addition for Appearance of Turbidity in Ethanolic Solutions of 8% w/w Eudragit® Polymers (n = 3)

Polymer Type	Temperature (°C ± SD)	Amount of Water (ml ± SD)	Ethanol/Water Ratio (w/w)
L100	42.3 ± 0.2	138.2 ± 1.6	1:1.38
S100	45.2 ± 0.3	85.3 ± 2.5	1:0.85
RL	46.2 ± 0.2	68.7 ± 1.3	1:0.68
RS	46.9 ± 0.1	55.0 ± 2.0	1:0.55

Physicomechanical Properties

From the size results (Table III) it can be seen that d_g of ibuprofen alone (reference sample) is slightly higher than that of agglomerates prepared in the presence of polymers, with the same amount of ibuprofen (ibuprofen/polymer 80 : 8 g), except in the case of Eudragit® RL. Also, the results in Table III show that, in general, d_g increases with increasing drug/polymer ratio for the cases of L100 and RL but decreases in the cases of S100 and RS, with the exception of S100 at low drug/polymer ratio (35 : 8). Furthermore, σ_g for all the agglomerates prepared in the presence of polymer is lower than that of the reference sample, except in the cases of water-soluble polymers (S100) at low drug/polymer ratio (35 : 8), indicating the presence of large and small agglomerates in smaller proportion.

Agglomeration is known to increase with increasing supersaturation because increased supersaturation leads to higher nucleation rates and to a higher concentration of microcrystals. This in turn leads to the aggregation of the microcrystals, which facilitates the extensive binding of the aggregates into agglomerates. Table II shows that the polymer solubility decreases at temperatures higher than the crystallization point of ibuprofen in Table I. Therefore, assuming that the separated polymer facilitates agglomeration of the developed ibuprofen microcrystals and that ibuprofen added in higher amounts increases the number of microcrystals and, therefore, the frequency of collisions, an increase in d_g is expected with increases in the amount of both ibuprofen and polymer. The unexpected size decrease of agglomerates in the presence of polymers and with increasing drug/polymer ratio may be attributed to changes in the habit and size of ibuprofen microcrystals caused by polymer presence. Also, the decrease of d_g, with decreasing mass fraction of S100 and RS, may indicate that their binding ability is adequate to counteract the effect of increased frequency of collisions caused by the addition of ibuprofen. On the contrary, the polymers RL and L100 should have smaller binding ability. So, the effect of frequency of collisions is predominant. The great difference in agglomerate size between L100 and RL confirms the ef-

Table III. Micromeritic Properties and Flow Parameters of Ibuprofen Spherical Crystal Agglomerates Prepared with Different Eudragit® and Increasing Drug/Polymer Ratio

Eudragit® Type and Drug/Polymer Ratio (g/g)		Particle Size		Particle Shape (n = 200)		Density (g/ml) (n = 3)		Compressibility Index (%)	Angle of Repose[d] (θ°)
		d_g (μm)	σ_g	Roundness[a]	Df[b]	Bulk[c]	Tapped[c]		
—	80/0	1150	0.652	7.9	1.07	0.39	0.45	13.2	58.5
S100	35/8	1110	0.806	2.7	1.19	0.32	0.35	7.9	34.5
	50/8	2000	0.650	2.8	1.26	0.36	0.39	5.4	34.5
	65/8	1910	0.492	4.4	1.26	0.26	0.28	8.1	41.0
	80/8	975	0.482	7.6	1.22	0.27	0.31	11.9	44.0
L100	35/8	550	0.672	3.3	1.26	0.19	0.23	17.2	34.5
	50/8	725	0.589	4.6	1.26	0.21	0.25	16.7	45.0
	65/8	760	0.559	5.5	1.25	0.24	0.28	12.2	21.0
	80/8	810	0.493	7.3	1.23	0.23	0.28	16.8	34.5
RS	35/8	1400	0.464	2.6	1.25	0.26	0.29	10.8	55.5
	50/8	1250	0.400	3.8	1.27	0.25	0.30	14.2	54.5
	65/8	1200	0.491	3.9	1.29	0.24	0.27	12.4	55.5
	80/8	1100	0.436	5.0	1.30	0.24	0.28	12.7	42.5
RL	35/8	1430	0.419	3.9	1.18	0.26	0.32	14.2	58.0
	50/8	1490	0.463	5.9	1.21	0.25	0.30	15.9	56.0
	65/8	1700	0.486	6.5	1.18	0.23	0.28	14.1	48.0
	80/8	1850	0.397	7.2	1.16	0.26	0.30	13.2	50.5

[a] SD < 1.0.
[b] SD < 0.05.
[c] SD < 0.1.
[d] SD < 2.0.

fect of supersaturation. Supersaturation should be accelerated as a result of the decrease of ibuprofen solubility by L100, and the size of microcrystals should be smaller and the collisions weaker. Therefore, we can conclude that the effect of polymer on the agglomerate size depends on its nature and the interactions with the ibuprofen microcrystals formed.

The shape results (Table III) show that roundness of all the spherical agglomerates prepared in the presence of polymer is lower and fractal dimension, D_f, is greater than the value of the reference sample. Taking into account that lower roundness value means greater sphericity, whereas higher fractal dimension means increased surface roughness, we can say that the presence of polymer contributes to improved sphericity and increased surface roughness of the agglomerates. Also, the roundness results (Table III) show that sphericity, in general, is improved with the increase in the mass fraction of polymer.

Improvement of sphericity may be attributed to coating of the microcrystals before their binding into agglomerates, which can result in improved symmetry of packing and equal agglomerate dimensions. The increase in surface roughness should be attributed to changes of habit and packing of the microcrystals developed. SEM photomicrographs show loose structure of acicular microcrystals for the reference sample [Fig. 3(a)], closer and continuous packing of tabular microcrystals for S100 and L100 [Fig. 3(b) and (c)], and discontinuous arrangement of prismatic ibuprofen microcrystals and particles for the water-insoluble RS or RL polymers [Fig. 3(d) and (e)].

The flow parameters (Table III) show that the bulk and tapped density of all the spherical crystal agglomerates prepared in presence of any type of Eudragit® is lower than that of the reference sample, although their sphericity is higher and their size is greater for most cases. Therefore, the reduction in bulk and tapped density should be related to the intraparticle porosity or particle density (Table IV) and to the surface roughness. As far as compressibility index, C.I. %, and the angle of repose values are concerned (Table III), it is seen that the last are smaller for all the cases of agglomerates prepared in the presence of polymer than those of the reference sample. The C.I. % values are lower than those of the reference sample, except in the cases of Eudragit® L100 and RL for almost any drug/polymer ratio. The decrease in the angle of repose is probably due to improved sphericity, and the increase of C.I. % for the latter cases should be attributed to the smaller particle size (for L100) and to the relatively small improvement in sphericity (for the RL case mentioned previously).

Regarding the density and porosity results (Table IV), it can be seen that true density values are higher and particle density values are lower than that of the reference sample, except in the case of Eudragit® S100 at low drug/polymer ratio (35 : 8). The increase in true density of agglomerates is expected because for all the methacrylic polymers used the true density is greater (1.2–1.5 g/ml) than that of ibuprofen (1.1 g/ml). In contrast, the lower particle density of agglomerates relative to that of the reference sample (Table IV) should be attributed to the increased intraparticle porosity.

Intraparticle porosity, ε_{intra}, given in Table IV, is generally higher than that of the reference sample, except for S100 in a low drug/polymer ratio (35 : 8), whereas interparticle porosity, ε_{inter}, shows positive and negative deviations (30%). The increase in intraparticle porosity corresponds to pores with diameter between 40 and 12 μm or smaller than 12 μm. Only for the agglomerates prepared in presence of Eudragit® RS and those prepared with Eudragit® RL in a high drug/polymer ratio (80 : 8) is the proportion of small pores, $\varepsilon_{<12}$, lower than that of the reference sample. No correlation was observed between the intraparticle porosity and the drug/polymer ratio, except in the case of Eudragit® S100 in which intraparticle porosity increases with drug/polymer ratio. The mean pore diameter is larger than that of the reference sample in almost all the cases of agglomerates prepared in presence of Eudragit® polymers.

The increase of pore diameter in combination with the increase in intraparticle porosity caused by the polymer indicates the absence of polymer deposition in the empty spaces between microcrystals in the agglomerates. Therefore, these increases should be attributed to coating and habit alteration of the ibuprofen microcrystals comprising the agglomerates. Coating is probably developed before binding into spherical agglomerates, leading to greater resistance of rearrangement and looser packing after collisions.

The compression behavior of the spherical agglomerates is expressed as parameters of the Heckel equation,[18] namely, the increase in packing density at the early stages of compression, D_B, and the yield pressure, P_y, given in Table IV. Also, representative Heckel plots are shown in Figure

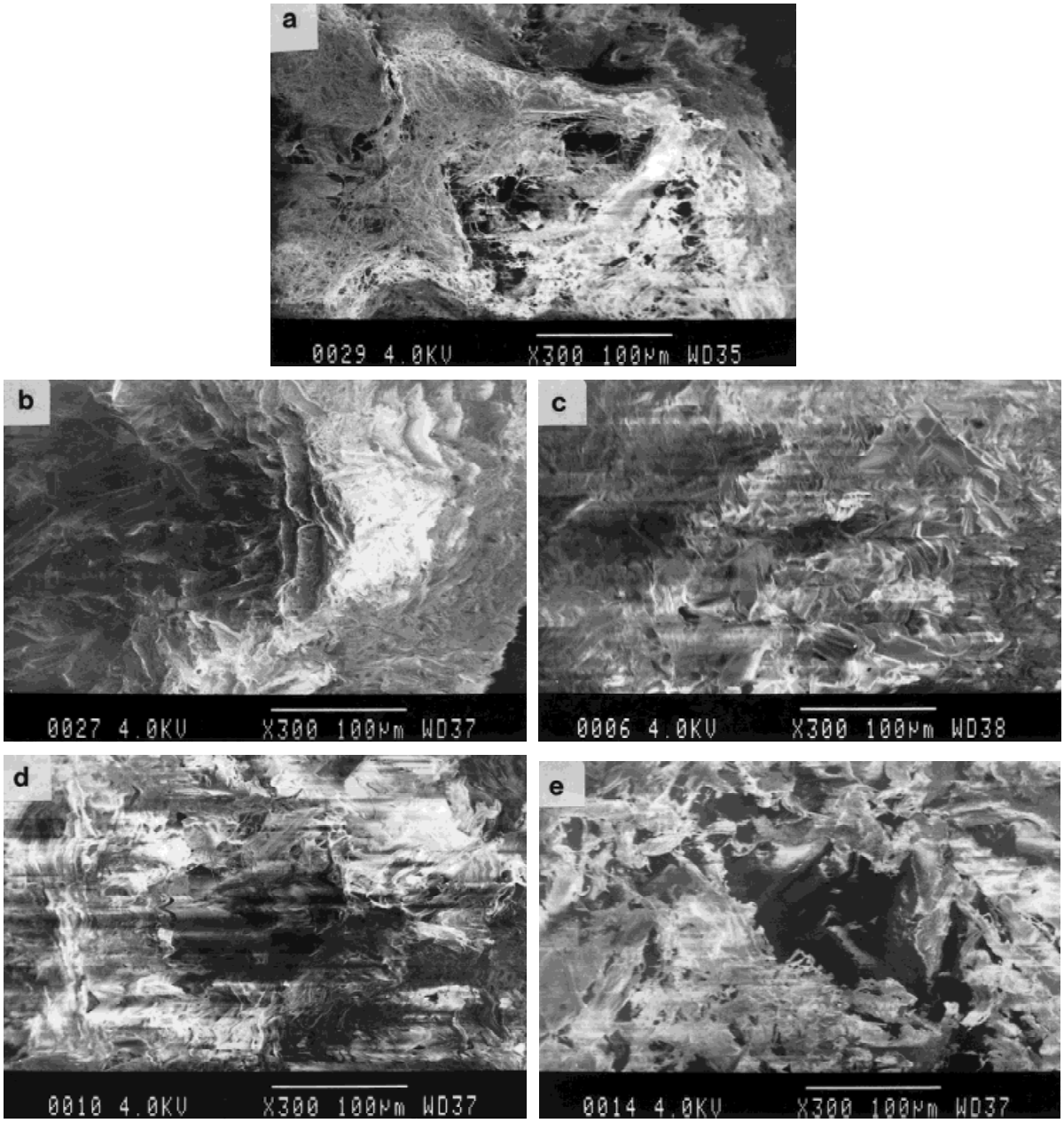

Figure 3. SEM photomicrographs of spherical crystal agglomerates prepared in presence of different Eudragit® polymers at drug/polymer ratio 80/8 g (key as in Figure 2).

4. D_B has been obtained from the difference between the packing fraction corresponding to the intercept of the extrapolated intermediate linear part of Heckel plots (Fig. 4) and that corresponding to tapped density. The yield pressure, P_y, is the reciprocal of the slope in the linear part corresponding to pressure range between 20 and 80 MPa.

From the results in Table IV, it is seen that D_B, for all the agglomerates prepared in presence of polymer, is higher than that of the reference sample, except in the case of S100 with low drug/polymer ratio (35 : 8 and 50 : 8 g). Also, the increase of D_B does not seem to be related to sphericity and surface roughness changes. Therefore, it should be related to particle size and particle density or intraparticle porosity. The yield pressure for all the agglomerates prepared in the presence of polymer is higher than that of the reference sample, except for the case of Eudragit®

Table IV. Parameters of Porosity and Compression Behavior (Heckel's Equation) for Ibuprofen Spherical Crystal Agglomerates Prepared with Different Eudragit® and Increasing Drug/Polymer Ratio (n = 3)

Eudragit Type and Drug/Polymer Ratio (g/g)		Density (g/ml)		Porosity (%)				Pore Mean Diameter (μm)	Heckel Parameters	
		True[a]	Particle[a]	ε_{inter}	ε_{intra}	ε_{40-12}	$\varepsilon_{<12}$		D_B[b]	P_y (MPa) (mean ± SD)
—	80/8	1.076	0.733	51.9	31.9	21.7	10.2	16.0	0.412	20.2 ± 3.1
S100	35/8	1.116	0.791	55.7	29.1	17.5	11.6	18.0	0.373	49.7 ± 9.6
	50/8	1.109	0.729	46.5	34.3	20.0	14.3	17.0	0.373	54.1 ± 6.4
	65/8	1.106	0.632	55.7	42.8	26.9	15.9	18.5	0.511	47.3 ± 9.4
	80/8	1.085	0.618	49.8	44.1	29.8	14.3	18.0	0.495	30.6 ± 4.8
L100	35/8	1.113	0.635	63.8	42.9	28.3	14.6	19.0	0.481	51.2 ± 8.0
	50/8	1.103	0.596	56.7	55.0	34.8	20.2	14.5	0.563	57.1 ± 8.8
	65/8	1.081	0.632	55.7	41.5	29.0	12.5	19.5	0.478	36.9 ± 8.5
	80/8	1.094	0.612	54.2	44.1	27.7	16.4	20.0	0.471	37.3 ± 9.4
RS	35/8	1.091	0.695	58.3	36.3	33.6	2.7	19.5	0.517	38.6 ± 8.5
	50/8	1.080	0.682	61.6	37.6	25.9	11.7	20.0	0.485	25.9 ± 2.9
	65/8	1.085	0.634	57.4	41.5	35.3	6.2	18.0	0.470	21.2 ± 2.9
	80/8	1.081	0.682	64.2	37.7	27.6	10.1	18.0	0.536	24.8 ± 5.3
RL	35/8	1.101	0.450	38.9	59.2	21.1	38.1	17.0	0.577	48.6 ± 9.3
	50/8	1.091	0.539	44.3	50.6	20.1	30.5	16.5	0.549	35.9 ± 8.1
	65/8	1.083	0.486	42.4	55.2	21.4	33.8	17.0	0.465	18.6 ± 2.2
	80/8	1.080	0.682	46.0	36.8	31.9	4.9	19.0	0.474	17.2 ± 1.2

[a] SD < 0.001.
[b] SD < 0.1.

RS and RL at high drug/polymer ratio (65 : 8 and 80 : 8). For the last cases the polymer loss is great and the yield pressure, P_y, is similar to that of the reference sample. Furthermore, the yield pressure, P_y, in general, increases with the mass fraction of the polymer.

The brittleness and the incorporation of the polymer should determine the increase of yield pressure. It is known that Eudragit® L100 and S100 are less plastic and more brittle than ibuprofen and Eudragit® RS and RL. Brittle fracture indexes reported in literature are 1.60 for L100, 1.20 for S100, and 0.07 for RL and RS,[19] whereas that for ibuprofen is 0.06.[20]

CONCLUSIONS

From the preceding it can be concluded that when solvent-change technique is applied with ethanol and water as miscible solvents for the spherical crystal agglomeration of ibuprofen in presence of methacrylic (Eudragit®) polymers the following apply:

(a) Crystal formation and growth changes occur because of alterations of the metastable zone caused by solubility changes, whereas the incorporation of drug and polymer into

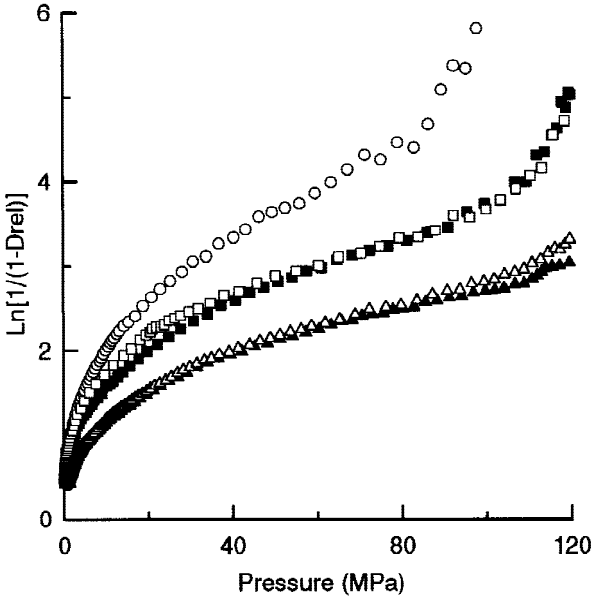

Figure 4. Heckel plots of spherical crystal agglomerates prepared in presence of different Eudragit® polymers at drug/polymer ratio 35/8 g (key as in Figure 1).

agglomerates and the crystal yield are altered by the polymer's solubility and micellization.

(b) The effect on the agglomerates' size depends on the nature of the polymer, whereas sphericity, surface roughness, and intraparticle porosity increase, in general, with the polymer presence because of changes in habit and growth rate of ibuprofen microcrystals and to their coating before binding into spherical agglomerates.

(c) Flow behavior and densification of agglomerates at low compression are determined by the particle density or intraparticle porosity and size changes, whereas their deformation under higher compression pressure, expressed as yield pressure, P_y, is determined by the brittleness and the incorporation of the polymer.

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