Drug Development and Industrial Pharmacy, 27(8), 847–855 (2001)

RESEARCH PAPER

Micromeritic and Packing Properties of Diclofenac Pellets and Effects of Some Formulation Variables

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ABSTRACT

The effects of two common diluents (microcrystalline cellulose and calcium phosphate dihydrate), two binding agents (gelatin and methacrylic polymer), and spheronization on the micromeritic (size, shape, density), flow, and packing properties of sodium diclofenac pellets were examined. The shape was assessed as the aspect ratio and was correlated to the flow rate and to the deviation of the tapped porosity from the value of 26%, which corresponds to the ideal rhombohedral packing of spheres. It was found that porosity deviation decreased greatly with spheronization, but it increased with binder addition. Porosity deviation was proportional to the aspect ratio, while flow rate decreased logarithmically with porosity deviation. Porosity deviation may be a useful index for monitoring the quality of pellets, similar to the aspect ratio, as a successful, simple, and indirect indication of sphericity and of surface roughness as well.

Key Words: *Aspect ratio; Flow rate; Pellets; Rhombohedral packing; Spheronization*

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INTRODUCTION

Multiple-unit dosage forms, especially pellets, offer many advantages over single-unit forms. Pelletization is mainly performed to obtain spherical particles because sphericity is important for the quality of the coating applied and for the dose uniformity of the final forms. Therefore, sphericity of pellets can be regarded as a quality indicator for the pelletization process (1).

Different methods have been suggested in the literature for the quantification of the sphericity of pellets, and most of them are based on two-dimensional microscopic measurements or on projected area (2–4). Only the Heywood (5) coefficient and a factor that was suggested by Podczeck and Newton (6) describe the three dimensions of particles. Also, the indirect method that was proposed by Erikson et al. (7,8) combines projected area and surface area obtained by permeametry as measurements of two and three main dimensions, respectively. The projected and the surface area measurements, more or less, require sophisticated techniques and data processing. Thus, simpler methods would be more suitable.

In the study described in this article, two simple shape factors were used. One quoted in many papers is based on the length and breadth (elongation or aspect ratio), and the other is based on the relative deviation from the rhombohedral packing during tapping, corresponding to 26% total interparticle porosity (9). The latter may be valid because the shape of a spheronized pellet could vary from spherical to round-edged cylindrical (dumbbell, ellipse, rope, sphere with cavity), while the size shows a narrow distribution (1,10).

Many formulation and processing variables may affect the shape and other micromeritic properties of pellets obtained by wet granulation and spheronization, as well as their flow and packing during capsule filling or tableting (11–18). Among the formulation variables are the type and proportion of excipients used (11–14) and the water content (11–16), while the processing variables include the type and speed of the friction plate and the residence time in the spheronizer (17,18). A great deal of time and effort would be required for an exhaustive study of all the variables related to the shape and other micromeritic properties (size, porosity, and surface roughness) and to the flow and packing during handling. Therefore, a simple method for the quantification of pellet sphericity should be useful for industrial quality monitoring.

In the work described here, we examined the effects of two common diluents (microcrystalline cellulose and calcium phosphate dihydrate), two binding agents (gelatin and methacrylic polymer), and the spheronization process on the micromeritic and packing properties in the production of sodium diclofenac pellets. Particularly, we compared the sphericity assessed on the basis of aspect ratio and on the basis of deviation of packing from the ideal closest (rhombohedral) packing of uniform monodispersed spheres. Also, we correlated them with the flow rate through an orifice.

EXPERIMENTAL

Materials

The following materials were used for the preparation of pellets: diclofenac sodium (Roig Farma, Spain); microcrystalline cellulose (Avicel PH-102, FMC, Cork, Ireland); dicalcium phosphate dihydrate (Emcompress, E. Mendell, New York); gelatin 80-100 blooms (Panreac, Spain); poly(methacrylic acid, methylmethacrylate) 1 : 1 (Eudragit® L30D-55, Röhm Pharma, Darmstadt, Germany); triethyl citrate (Morflex, Inc., North Carolina); and distilled water.

Preparation of Pellets

For pellet preparation, 66.6 g of diclofenac sodium was mixed with 133.4 g of diluent (Avicel, Emcompress, or a mixture of the two) in a planetary mixer for 10 min. This time was selected to achieve uniform distribution, as assessed by sampling and spectrophotometric assay of diclofenac. Then, a given volume of granulating liquid (water and aqueous solution, 9% or 18% w/v for gelatin and 10% or 30% w/v for Eudragit) was gradually added (over 5 min) with mixing. For mixtures containing Avicel only, 130 ml of granulating liquid was used; 90 ml was used for mixtures of Avicel and Emcompress; and 65 ml was used for mixtures containing Emcompress only. Triethyl citrate was added at 10% w/w proportion of Eudragit. Mixing was continued for an additional 5 min after the addition of granulating liquid. The wet mass was passed through an oscillating granulator (Erweka type FGS, Germany) equipped with wire screen with a 1.5-mm aperture.

The wet granules (or two-thirds for some batches) were transferred to a 120-mm diameter spheronizer equipped with a crosshatch friction plate (Caleva 120, England). Spheronization was performed at 2000 rpm for 7 min. The spheroids and the nonspheronized wet granules (reference sample) were dried at 40°C for 12 h in a conventional laboratory oven after spreading on trays. The moisture content of all the granulations and pellets was monitored and kept to less than 3.5% w/w. Samples of 1 g and an infrared moisture balance were used (Mettler PM100 and LP16-M, Mettler Instruments, Greifensee, Switzerland). Heating at 105°C was applied until the change in weight was less than 0.2% in 2 min.

Characterization of Pellets

Size

For size characterization, 30-g samples of dried granules or pellets were sieved through a nest of sieves (CISA, Spain). Sieves with aperture sizes of 1.5, 1.0, 0.84, 0.71, 0.5, and 0.3 mm were used; the samples were shaken for 5 min on a vibrating shaker (CISA, Spain). The amount retained on each sieve was weighed and plotted as cumulative percentage frequency versus size (arithmetic mean of two successive screens) on log-probability scales. The geometric mean diameter d_g (or the size corresponding to 50% cumulative retained) and the geometric standard deviation σ_g (or the size ratio for 84%/50% retained) were noted.

Shape

The shape of pellets and granules was expressed as the aspect ratio and as the percentage deviation from ideal closest (rhombohedral) packing of uniform (monodispersed) spheres, corresponding to 26% total porosity (9). The aspect ratio of each individual particle is the ratio between the longest caliper distance and the caliper distance perpendicular to the longest one. It was determined for at least 50 pellets or granules using an Olympus optical microscope (magnification 10×) with a graticule in the eyepiece lens. The following equation was used:

$$\text{Percentage deviation of tapped porosity} = \left[\frac{\%\ \text{Total tapped porosity}}{26} - 1\right] \times 100$$

The total tapped porosity $e\%$ was calculated from the apparent particle density ρ_p and tapped density ρ_t:

$$e\% = \left[1 - \left(\frac{\rho_t}{\rho_p}\right)\right] \times 100$$

Scanning electron microphotographs were obtained in a JEOL 6400 (CAI Microscopia Electrónica Luis Bru, UCM) after coating with gold for confirmation of changes in the shape and the surface roughness of the pellets.

Density

The apparent particle density ρ_p of the pellets and granules was determined on a helium gas comparison pycnometer (Micromeritics 1305, USA). The loose bulk density ρ_b and tapped density ρ_t were measured in a PharmaTest volumeter (model PT TD, Germany) using a 100-ml measuring cylinder and applying 500 taps. This number of taps was selected because it was enough for equilibration in volume reduction of both pellets and granules.

Flow Rate

A conical plastic funnel (6.5 cm high, 9.1 cm top opening, and low circular orifice with 1.27 cm diameter) was used for the determination of flow rate. The time required for about 50 g of sample to flow was measured, and the flow rate was expressed in $g \cdot s^{-1}$. Five tests were run for each batch, and the mean value was recorded. Reproducibility of the method was assessed as the relative standard deviation percentage (RSD%) and was found to be less than 5%.

Packing Ability

The packing ability was evaluated from the changes in volume due to rearrangement and packing occurring during tapping in the PharmaTest volumeter and was expressed as Carr's compressibility index (19)

$$CC\% = \left[\frac{(\rho_t - \rho_b)}{\rho_t}\right] \times 100$$

and as the Hausner ratio (20)

$$HR = \frac{\rho_t}{\rho_b}$$

Flow rate, tapped density, and porosity deviation were evaluated for each batch of granules and pellets and for three size fractions obtained by sieving: small (0.1–0.5 mm), medium (0.5–0.84 mm), and large (0.84–1.5 mm).

RESULTS AND DISCUSSION

In Table 1, the results of the fundamental particle (micromeritic) properties of the granules and pellets (size, aspect ratio, and density) are given, together with the key code of formulation and the residence time in the spheronizer. Table 2 summarizes the properties of flow rate, packing ability, and porosity (total tapped porosity and porosity deviation), which depend on the micromeritic (particle) properties. Table 3 lists the results of flow rate, tapped density, and porosity deviation, evaluated for the three size fractions of each batch of granules and pellets.

From Table 1, we can say that the difference in mean geometric diameter d_g between the granules and corresponding pellets is within a range of $\pm 140\,\mu m$, but does not show any characteristic change with the spheronization or with the nature of diluent or binder used. The results of geometric standard deviation σ_g show that the size distribution of pellets was not as narrow as expected, probably because a conventional wet granulator was used for extrusion. From Table 1, it is also seen that σ_g decreased with spheronization, but increased with binder addition for both the binders and for both the diluents, as well as for their mixture. This indicates that, in general, binder addition, unlike spheronization, results in wider size distribution of pellets. Also, the aspect ratio of pellets decreased with spheronization and generally seemed to increase slightly with binder addition, but is close to the acceptable range for capsule filling, that is, less than 1.2 (21).

As far as the density is concerned, it depended on the composition or on the nature of the diluents employed. Incorporation of Emcompress resulted in increased density (apparent particle, bulk, and tapped), as expected. Also, bulk and tapped densities of all the spheronized granules (pellets) were higher than those of the corresponding nonspheronized granules, also as expected, due to the densification that occurred. Fig. 1 shows the difference in particle packing between granules and pellets.

The effect of addition and concentration of the binder on the bulk and tapped densities or on the densification differed and seemed to depend on the

Table 1

Fundamental Particle (Micromeritic) Properties of Granules and Pellets (Size, Aspect Ratio, Density) Together with the Key Code of Formulation and the Residence Time in the Spheronizer

Formulation Code[a]	Residence Time (min)	Size		Aspect Ratio	Density (g/ml)		
		d_g (μm)	σ_g		Apparent Particle	Bulk	Tap
A	0	854	1.20	1.75	1.392	0.35	0.44
A	7	851	1.10	1.06	1.392	0.76	0.85
AG_1	7	784	1.11	1.21	1.394	0.73	0.82
AG_2	7	800	1.14	1.47	1.394	0.66	0.74
AL_1	0	764	1.21	1.46	1.392	0.38	0.46
AL_1	7	844	1.10	1.22	1.392	0.72	0.78
AL_2	0	855	1.21	1.64	1.392	0.45	0.51
AL_2	7	993	1.13	1.11	1.392	0.73	0.80
EG_1	7	776	1.15	1.23	1.993	0.91	1.00
EG_2	7	868	1.12	1.32	1.993	0.95	1.05
AE	0	865	1.19	1.64	1.604	0.43	0.51
AE	7	891	1.11	1.17	1.604	0.87	0.98
AEG_1	7	853	1.13	1.21	1.693	0.81	0.93
AEG_2	7	858	1.14	1.23	1.693	0.81	0.90

[a]Composition of pellets: A, Avicel; E, Emcompress; G, gelatin; L, Eudragit. Subindex for G and L is related to the proportion incorporated in the formulation (1 is low and 2 is high).

Table 2

Flow Rate, Porosity (Total Porosity and Porosity Deviation) and Packing Ability of Granules and Pellets

Formulation Code[a]	Residence Time (min)	Flow Rate[b] ($g.s^{-1}$)	Total Tapped Porosity (e%)	Porosity Deviation (%)	Carr's Compressibility Index (CC%)	Hausner Ratio (HR%)
A	0	11.1	68.4	163	20.4	1.26
A	7	26.6	38.9	50	10.6	1.11
AG_1	7	26.3	41.2	58	11.0	1.12
AG_2	7	21.5	46.9	80	10.8	1.12
AL_1	0	13.8	66.9	157	17.4	1.21
AL_1	7	25.6	44.0	69	7.7	1.08
AL_2	0	15.9	63.3	144	11.8	1.13
AL_2	7	27.2	42.5	64	8.7	1.09
EG_1	7	34.8	49.8	92	9.0	1.10
EG_2	7	21.5	47.3	82	9.5	1.10
AE	0	12.2	68.2	162	15.7	1.19
AE	7	29.9	38.9	50	10.7	1.12
AEG_1	7	29.3	45.1	73	12.9	1.15
AEG_2	7	29.4	46.8	80	10.0	1.11

[a]Composition of pellets: A, Avicel; E, Emcompress; G, Gelatin; L, Eudragit. Subindex for G and L is related to the proportion incorporated in the formulation (1 is low and 2 is high).
[b]Relative standard deviation $< 5\%$.

Table 3

Flow Rate, Tapped Density, and Porosity Deviation from that Corresponding to Ideal Rhombohedral (26%) for the Three Size Fractions of Each Batch of Granules and Pellets

		Size Fraction of Granules and Pellets								
		0.1–0.5 (mm)			0.5–0.84 (mm)			0.84–1.5 (mm)		
Formulation Code[a]	Residence Time (min)	Flow Rate[b] (g/s)	Tap Density (g/ml)	Porosity Deviation (%)	Flow Rate[b] (g/s)	Tap Density (g/ml)	Porosity Deviation (%)	Flow Rate[b] (g/s)	Tap Density (g/ml)	Porosity Deviation (%)
A	0	13.0	0.43	166	10.4	0.40	174	9.5	0.37	182
A	7	32.0	0.91	33	25.5	0.87	44	23.7	0.83	55
AG_1	7	26.3	0.81	61	23.8	0.80	64	20.8	0.82	58
AG_2	7	21.5	0.68	97	17.2	0.71	89	17.6	0.74	80
AL_1	0	8.5	0.42	169	11.0	0.40	174	9.4	0.43	166
AL_1	7	23.1	0.79	66	18.8	0.75	77	22.1	0.76	75
AL_2	0	13.3	0.49	149	11.7	0.50	146	11.6	0.48	152
AL_2	7	30.4	0.82	58	28.1	0.76	75	20.6	0.74	80
EG_1	7	39.2	1.01	90	37.0	0.98	95	31.3	0.96	99
EG_2	7	29.2	0.99	94	25.6	1.06	80	30.1	1.03	86
AE	0	16.8	0.53	157	10.9	0.44	179	9.7	0.42	184
AE	7	22.5	0.92	73	28.7	0.96	54	26.9	0.97	52
AEG_1	7	25.3	0.93	73	21.6	0.89	82	22.8	0.91	78
AEG_2	7	22.8	0.88	85	26.3	0.92	76	27.2	0.92	76

[a]Composition of pellets: A, Avicel; E, Emcompress; G, Gelatin; L, Eudragit. Subindex for G and L is related to the proportion incorporated in the formulation (1 is low and 2 is high).
[b]Relative standard deviation $< 5\%$.

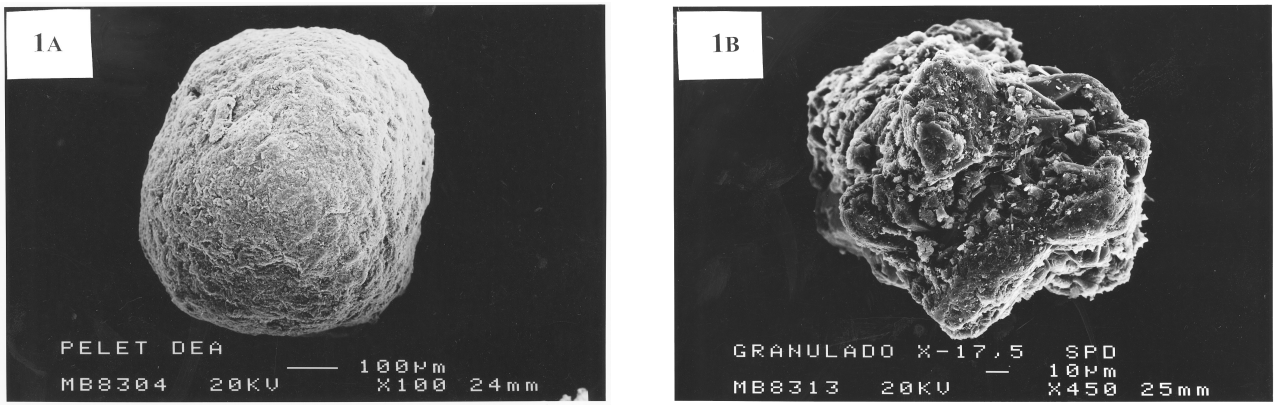

Figure 1. Scanning electron microphotographs of a pellet (1A) and a granule (1B).

nature of the diluent employed (Table 1). In formulations containing Avicel, the addition of both binders (gelatin and Eudragit) resulted in pellets of lower bulk and tapped densities. The effect of binder addition on Emcompress formulations could not be evaluated because it was not possible to prepare pellets without binder. Although granules can be obtained with diclofenac, Emcompress, and water only, they do not have enough strength for spheronization and therefore break into powder when spheronizing.

The increase of the binder concentration resulted in decreased bulk and tap densities, except in the cases of pellets containing Avicel with the binder Eudragit (AL_1 and AL_2) and of those that contained Emcompress with the binder gelatin (EG_1 and EG_2). This exception may be attributed to the relatively great difference in size for the aforementioned cases of pellets (from 844 to 993 µm and from 776 to 868 µm). For all the other pellets, the reduced bulk and tap densities with binder addition and increase of its concentration should be attributed to reduced densification since the pellet sizes were more or less similar.

The reduced densification of pellets due to binder addition and concentration may be caused by the difficulty in sliding of the particles in the wet agglomerates due to the presence of more viscous or jellified aqueous binder solution. This is in agreement with the porosity results shown in Table 2. The total porosity of pellets after tapping e% increased with the addition and concentration of binder for all the pellet formulations, except for the cases showing great size change (AL_1 and AL_2, EG_1 and EG_2), mentioned above. This general increase in total tapped porosity with binder addition and concentration cannot be related to the slight increase in geometric standard deviation σ_g of the pellets. Wider variation in the size would be expected to result in sifting of the smaller pellets between the larger pellets and finally to lower total porosity. Therefore, it should be attributed to the increased aspect ratio or elongation, shown in Table 1, or to the higher surface roughness of pellets due to looser packing of the particles in them.

It is known that ideal spheres or pellets of uniform size can assume either closest (rhombohedral) or loosest (cubic) packing, which correspond to 26% or 48% total porosity, respectively. The granules and real pellets are neither spherical nor uniform, and higher values of the total tapped porosity (deviating from the ideal closest packing, 26%) are usual. The results in Table 2 show a clear increase in porosity deviation with binder addition and concentration. As mentioned above, the porosity deviation of the pellets examined (Table 2) cannot be attributed to their mean size or to the size distribution (except for the cases AL_1, AL_2, EG_1, EG_2). Therefore, it should be attributed either to the texture and surface roughness of pellets or to their higher aspect ratio (elongation). Furthermore, the values of the compressibility index CC% and Hausner ratio HR% seem to change almost in parallel to that of porosity deviation and inversely to that of flow rate (Table 2), which was expected.

The flow rate of granules, and particularly of pellets, through a circular orifice should depend on the gravitational and frictional forces operating on

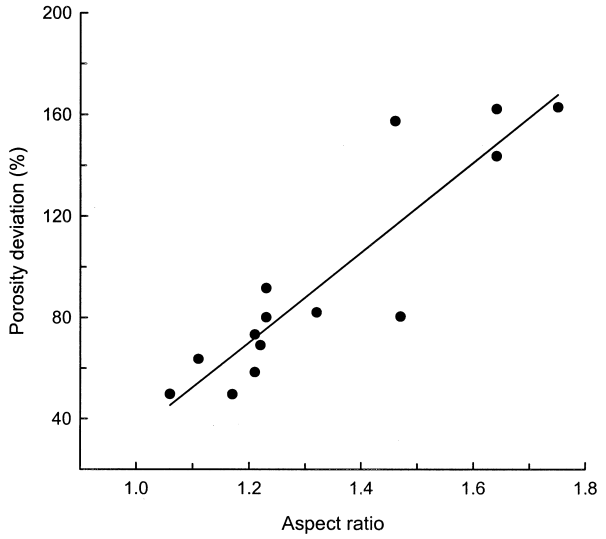

Figure 2. Relationship between aspect ratio and porosity deviation for the unfractionated pellets.

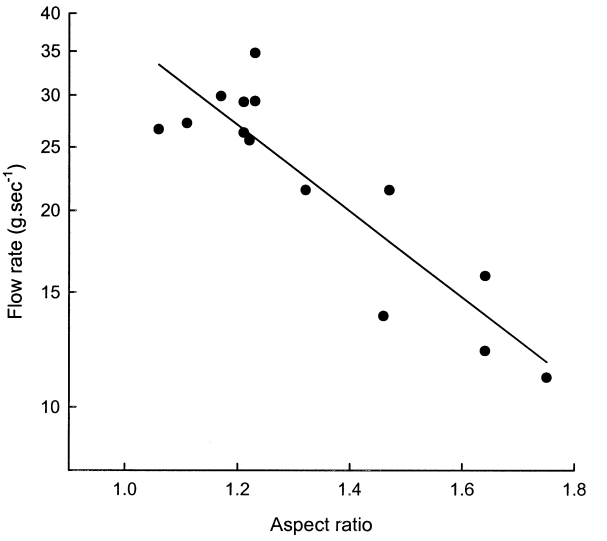

Figure 3. Logarithmic relationship between flow rate and aspect ratio for the unfractionated pellets.

them. The gravitational forces are determined from the size and the density, while the frictional forces depend on the size (or the number of contact points), on the shape (aspect ratio), and on the texture or surface roughness. Since size is assumed to be under control, the flow rate of the pellets may be related to the shape or aspect ratio and to the deviation of porosity, which may be an indication

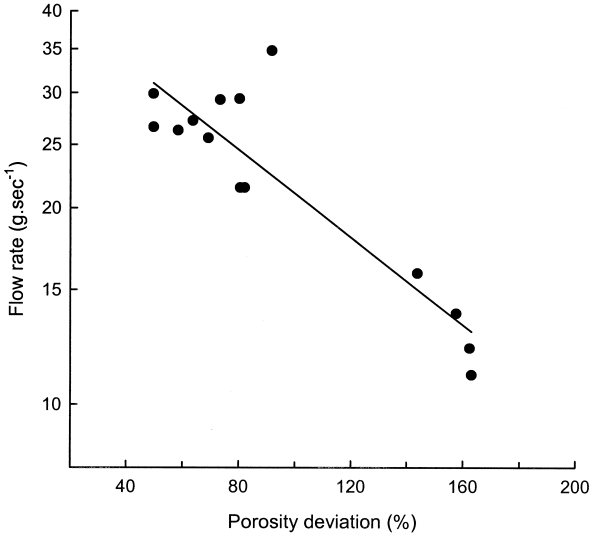

Figure 4. Logarithmic relationship between flow rate and porosity deviation for the unfractionated pellets.

of both the shape and the surface roughness of pellets. Fig. 2 shows the relationship between aspect ratio and porosity deviation for the unfractionated pellets. Fig. 3 shows the relationship between flow rate and aspect ratio, and Fig. 4 shows the relationship between flow rate and porosity deviation.

From Fig. 2, we see that porosity deviation was proportional to the aspect ratio, and its values have a much wider (double) range. The wider range of values may be due to the contribution of surface roughness in addition to the aspect ratio in the value of tapped porosity measured. From Figs. 3 and 4, we can see that flow rate decreased logarithmically with both aspect ratio and porosity deviation.

The logarithmic relation between flow rate and the parameters under examination (aspect ratio and porosity deviation) indicates that small changes in these parameters elicited great change in flow rate. The correlation coefficients in the relationships of the above three parameters are reasonable considering the wide size distribution of the pellets since they are not fractionated. It is known that flow rate and packing are affected greatly by the size and the size distribution of the particles as well.

Furthermore, considering that, according to Chopra et al. (21), the aspect ratio is sufficient to identify batches of pellets as suitable for filling in

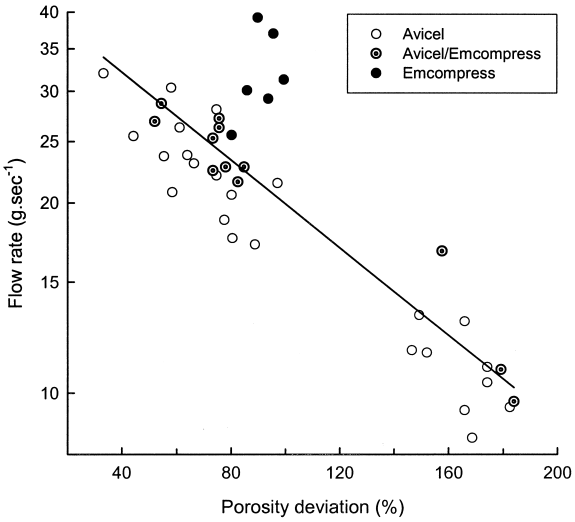

Figure 5. Logarithmic relationship between flow rate and porosity deviation for all the sieve fractions of granules and spheronized pellets.

capsules, these relationships may indicate that, similar to the aspect ratio, the porosity deviation could also be a useful index for monitoring the quality of pellets. Fig. 5 shows the relationship between flow rate and porosity deviation for all the sieve fractions of granules and spheronized pellets, independent of size. It is logarithmic and significant at a probability level $P = 0.0001$. Fig. 5 also shows that the highest deviation corresponds to pellets that contained only Emcompress as diluent. This indicates that the highest true density of Emcompress should be responsible for increased gravitational forces acting on pellets during their flow through the orifice and for the highest deviation in the flow rate. If we ignore the points generated by Emcompress alone, the correlation coefficient in the relationship between flow rate and porosity deviation (Fig. 5) increases to the value of 0.926. Furthermore, Fig. 5 also shows that the nature of the diluent, in general, affects the relationship between flow rate and porosity deviation because the corresponding points seem to be located in different parallel zones.

CONCLUSION

From the data presented, it may be concluded that spheronization of pellets results in a great decrease of the deviation of tapped total porosity from the value of 26%, while the binder addition generally results in increased porosity deviation. Deviation of tapped total porosity may be a useful index for monitoring the quality of pellets, similar to the aspect ratio, and may provide a successful and simple indirect index of their sphericity and surface roughness as well.

REFERENCES

1. Vervaet, C.; Baert, L.; Remon, J.P. Extrusion-Spheronisation. A Literature Review. Int. J. Pharm. **1995**, *116*, 131–146.
2. Chapman, S.R.; Rowe, R.C.; Newton, J.M. Characterization of the Sphericity of Particles by the One Plane Critical Stability. J. Pharm. Pharmacol. **1988**, *40*, 503–505.
3. Hellén, L.; Yliruusi, J. Process Variables of Instant Granulator and Spheroniser: III. Shape and Shape Distributions of Pellets. Int. J. Pharm. **1993**, *96*, 217–223.
4. Podczeck, F.; Newton, J.M. A Shape Factor to Characterize the Quality of Spheroids. J. Pharm. Pharmacol. **1994**, *46*, 82–85.
5. Heywood, H. Particle Shape Coefficients. J. Imp. Coll. Chem. Eng. Soc. **1954**, *8*, 25–33.
6. Podczeck, F.; Newton, J.M. The Evaluation of a Three-Dimensional Shape Factor for the Quantitative Assessment of the Sphericity and Surface Roughness of Pellets. Int. J. Pharm. **1995**, *124*, 253–259.
7. Erikson, M.; Nyström, C.; Alderborn, G. The Use of Air Permeametry for the Assessment of External Surface Area and Sphericity of Pelletized Granules. Int. J. Pharm. **1993**, *99*, 197–207.
8. Erikson, M.; Alderborn, G.; Nyström, C.; Podczeck, F.; Newton, J.M. Comparison Between and Evaluation of Some Methods for the Assessment of the Sphericity of Pellets. Int. J. Pharm. **1997**, *148*, 149–154.
9. Martin, A.; Bustamante, P.; Chun, A.C. *Physical Pharmacy*, 4th Ed.; Lea and Febiger: Philadelphia, 1993; 423.
10. Rowe, R.C. Spheronization: A Novel Pill-Making Process? Pharm. Int. **1985**, *6*, 119–123.
11. Baert, L.; Remon, J.P. Influence of Amount of Granulation Liquid on the Drug Release Rate from Pellets Made by Extrusion Spheronisation. Int. J. Pharm. **1993**, *95*, 135–141.
12. Pinto, J.F.; Buckton, G.; Newton, J.M. The Influence of Four Selected Processing and Formulation Factors on the Production of Spheres by Extrusion and Spheronisation. Int. J. Pharm. **1992**, *83*, 187–196.
13. Newton, J.M.; Chow, A.K.; Jeewa, K.B. The Effect of Excipient Source on Spherical Granules Made by

Extrusion-Spheronization. Pharm. Tech. Int. Biophys. **1992**, *4*, 20–28.
14. Law, M.F.L.; Deasy, P.B. Effect of Common Classes of Excipients on Extrusion-Spheronization. J. Microencapsulation **1997**, *14*, 647–657.
15. Varshosaz, J.; Kennedy, R.A.; Gipps, E.M. Effect of Binder Level and Granulating Liquid on Phenylbutazone Pellets Prepared by Extrusion-Spheronization. Drug Dev. Ind. Pharm. **1997**, *23*, 611–618.
16. Fielden, K.E.; Newton, J.M.; Rowe, R.C. The Influence of Moisture Content on Spheronization of Extrudate Processed by a Ram Extruder. Int. J. Pharm. **1993**, *97*, 79–92.
17. Baert, L.; Vermeersch, H.; Remon, J.P.; Smeyers-Verbeke, J.; Massart, D.L. Study of Parameters Important in the Spheronisation Process. Int. J. Pharm. **1993**, *96*, 225–229.
18. Wan, L.C.; Heng, P.W.S.; Liew, C.V. Spheronization Conditions on Spheroid Shape and Size. Int. J. Pharm. **1993**, *96*, 59–65.
19. Carr, R.L. Evaluating Flow Properties of Solids. Chem. Eng. **1965**, *18*, 163–168.
20. Hausner, H.H. Friction Conditions in a Mass Metal Powder. Int. J. Powder Metall. **1967**, *3*, 7–13.
21. Chopra, R.; Podczeck, F.; Newton, *J.M. Proc. 2nd World Meeting APGI/APV*, Paris; 1998, 161–162.

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