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Process variables of instant granulator and spheroniser: II. Size and size distributions of pellets

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Summary

The size and size distributions of pellets produced by continuous granulation and extrusion/spheronisation were evaluated. The effect of six process variables on two levels was studied. Pellet size was determined by image analysis, but also manually from enlarged photographs. The amount of pellets needed to give a reliable and representative mean size value was studied. For heterogeneous batches an appropriate number of pellets to be measured would be 800, while in the case of a homogeneous batch 200 pellets might be enough. The effect of size of the granule outlet of the instant granulator and speed of the spheroniser friction plate was most significant on all size parameters – when a larger granule outlet (consequently lighter kneading during granulation), and a higher speed of the friction plate were used, pellets were smaller, and the distributions were narrower. A greater load of spheroniser and a longer residence time in the spheroniser reduced the size of pellets.

Introduction

Pelletisation is a rather complicated multivariable process compared to typical wet granulation methods such as high shear granulation or fludized bed granulation (Schæfer, 1988). Pelletisation has, however, significant advantages over the other techniques. A successful process yields spherical, dense particles which have a narrow size distribution, and optimal packing and flow properties (Conine and Hadley, 1970; Reynolds, 1970).

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Compared to granules, spherical particles have low surface area to volume ratio and, therefore, are ideal for the application of film-coatings to optimize drug release kinetics and thus improve the in vivo behaviour of the products (Rowe, 1985; Ghebre-Sellassie, 1989). The uniformity of coating requires that the size distribution of pellets is narrow, and remains as unchanged and homogeneous as possible from batch to batch; the size and size distribution of pellets affect the coating capture of the cores and thereby the release kinetics of the drug (Wesdyk et al., 1990; Iley, 1991).

The objective of the present study was to investigate the size and size distribution of pellets produced using a continuously operating instant granulator, and a spheroniser; the effect of alto-

gether six independent process variables was evaluated. Attention was also paid to the general evaluation of measured, derived and geometric size of pellets, and to the amount of pellets needed to give a reliable and representative mean size parameter value.

Materials and Methods

Materials

Mannitol (75%, Merck, Germany), microcrystalline cellulose (20%, Emcocel 50M, Edward Mendell Co., U.S.A.), caffeine (5%, Boehringer Ingelheim, Germany) and distilled water (35 or 38% on the basis of dry weight) were used as starting materials, all of Ph. Eur. grade.

Preparation of pellets

The continuous granulation and extrusion/spheronisation method was used in the preparation of pellets (Nica System AB, Mölndal, Sweden). For the study of the effect of process variables, the complete 2^6 study design was used. The independent variables were the amount of water, the speed of powder addition, the size of granule outlet in the granulator, and the load, the residence time and the speed of the friction plate in the spheroniser. The repeatability of the process was tested by two randomized control points. The extrusion operation was kept constant to isolate the effect of the granulation stage. The description of the equipment and the preparation of pellets were discussed in detail in the preceding article (Hellén et al., 1993c).

Size of pellets

The size of pellets was determined by three types of size parameters: size measured by optical microscopy (Olympus Stereo Zoom Microscopy, SZH-ILLK, Olympus Optical Ltd, Tokyo, Japan) and image analysis (OPT/IA, Kontron Vidas +, Kontron Bildanalyse GmbH, Munich, Germany), derived size parameters calculated from measured data, as well as manually determined geometric size parameters measured from enlarged micrographs.

Measured parameters

The following five characteristics were measured by optical microscopy and image analysis from each pellet: minimum (d_{min}) and maximum (d_{max}) of the distances between 32 pairs of parallel tangents to the projected outline of the pellet in μm; perimeter (perim) of the object which is the length of the outline of the projection in μm; convex perimeter (cperim) of the object which is the length of a regular polygon with 64 corners streched around the object; two-dimensional area of the projection of the pellet in μm^2.

At least 800 pellets from each of the 66 batches were measured. The method employed has been described by Hellén et al. (1993a).

Derived parameters

From measured size data, new parameters indicating size – diameters, surface areas and volumes – were calculated by using various MathCAD v3.0 documents (MathSoft Inc., Cambridge, MA, U.S.A.) (Hellén et al., 1993a). From distributions of measured and derived parameters, means, standard deviations, 10%, 50% (median) and 90% fractiles, as well as 90–10% widths and spans (90–10%)/50% were calculated.

Geometric parameters

From six pellets, the shortest width ($d_{min,geom}$) and the longest length ($d_{max,geom}$) were measured, and geometric average diameter ($d_{ave,geom}$) was calculated from these. The geometric surface area (A_{geom}) and geometric volume (V_{geom}) were determined by measuring from enlarged photographs the height of each pellet from approx. 100 points. The numerical values for the parameters A_{geom} and V_{geom} were calculated using the following equations:

$$A_{geom} = dx4\Sigma\pi(y_i/2)^2 \quad (1)$$

$$V_{geom} = dx4/3\Sigma\pi(y_i/2)^3 \quad (2)$$

where dx is the step length in the x-direction, and y_i denotes the height of the pellet corresponding to the x value x_i. This has been visualized in Fig. 1. Thus, the value $y_i/2$ corresponds to the vertical radius of the pellet at point x_i.

Results and Discussion

Size of six individual pellets

In the preceding paper (Hellén et al., 1993c), all 66 pellet batches were classified by visual investigation into six shape groups (I–VI) so that the batch which had the roundest pellets represented group VI. Fig. 2a–f shows one pellet from each shape group. The measured (OPT/IA), derived and manually measured geometric size parameter values for these pellets are presented in Table 1.

Diameters

The maximum diameter of pellets, measured by image analysis, varied from 2.89 to 1.03 mm, separating the six pellets (A–F) clearly from each other (Table 1 and Fig. 2). Instead, no significant difference in d_{min} values was found. This is obvious since earlier studies have also verified that the width of pellet is close to the size of the extruder screen diameter irrespective of the length of the pellet (Conine and Hadley, 1970; Hellén et al., 1993a).

Values of the derived size parameters d_{ave} and d_{area} were quite similar. The parameter d_{per} followed the d_{max} values most closely, while d_{cper} clearly underestimated the size of pellet.

The geometric d_{max} values for pellets were very close to those measured by image analysis. This clearly indicates that image analysis is able to determine the longest diameter of a pellet. Instead, the $d_{min,geom}$ values were 1–12% lower than those measured by image analysis. That is due to the measurement routine using pairs of tangents – tangents follow the outer line of a pellet and cannot reach the depressions. Pellets in Fig. 2b and c are only slightly dog-bone shaped, but differences in widths between d_{min} and $d_{min,geom}$ are as great as 12 and 11%, respectively. In the case of the roundest pellet (F) the values are about the same.

The diameter parameters of the most elongated pellet A differed from each other radically, while those of the roundest pellet F were actually the same. The size of a spherical homogeneous particle is uniquely defined by its diameter (Allen, 1990). Thus, as has been found earlier, derived diameter parameters can be used when evaluating the sphericity of pellets (Hellén et al., 1993b) – if all diameter parameters are equal, the particle is spherical. In the case of the roundest pellet the ratio of diameters $d_{min} : d_{max} : d_{area}$ was 0.94 : 1.00 : 0.95, while in the case of most elongated pellet it was 0.37 : 1.00 : 0.62 – far from the ideal ratio 1.00 : 1.00 : 1.00.

Surface areas and volumes The size of a pellet directly affects the surface area and, consequently, the amount of coating necessary for the desired film thickness and drug release kinetics. There are three methods of measuring the surface area of pellets: calculations from the size of pellets, gas adsorption and air permeability (Mehta, 1989). In this study the surface area of a pellet was estimated from its diameters and also geometrically.

In the case of the most elongated pellet A, differences between surface area parameters were great, varying from 3.5 to 26.2 mm^2. None of the calculated values was similar to the geometric value. For the roundest pellet F, all surface areas except A_{dcper} were close to each other and close to the geometric value 3.0 mm^2.

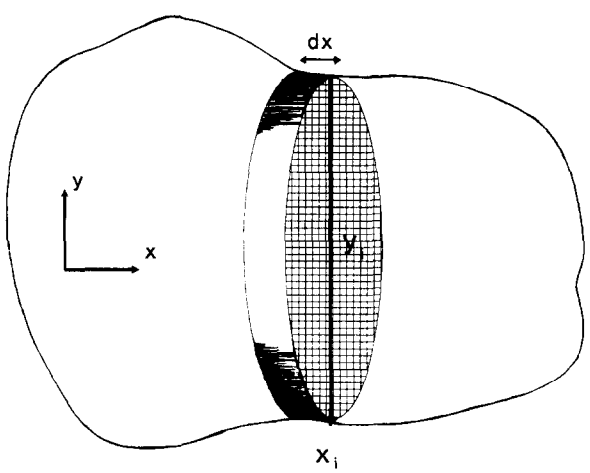

Fig. 1. Method for calculating the geometric surface area and volume of a pellet (dx, step length; y_i, height of a pellet corresponding to the x value x_i).

The same tendency, but even more clearly, was seen for the volume. In studying the surface area or volume of quite spherical pellets it seems that the most reliable size parameters – compared to geometric values – are those derived from the measured two-dimensional area derivatives $A_{d_{area}}$ and $V_{d_{area}}$. In both cases the difference from the geometrically determined value was less than 3%.

Due to the geometric definition of surface area of pellet the porosity and surface morphology have not been taken into consideration. Therefore, the surface area and volume values calculated apparently give more information about the shape of a pellet, i.e., difference from a perfect sphere, than the accurate values necessary for, e.g., film coating. In the case of a perfect sphere, which has a diameter of 1.00 mm, the surface area to volume ratio should be 6.00

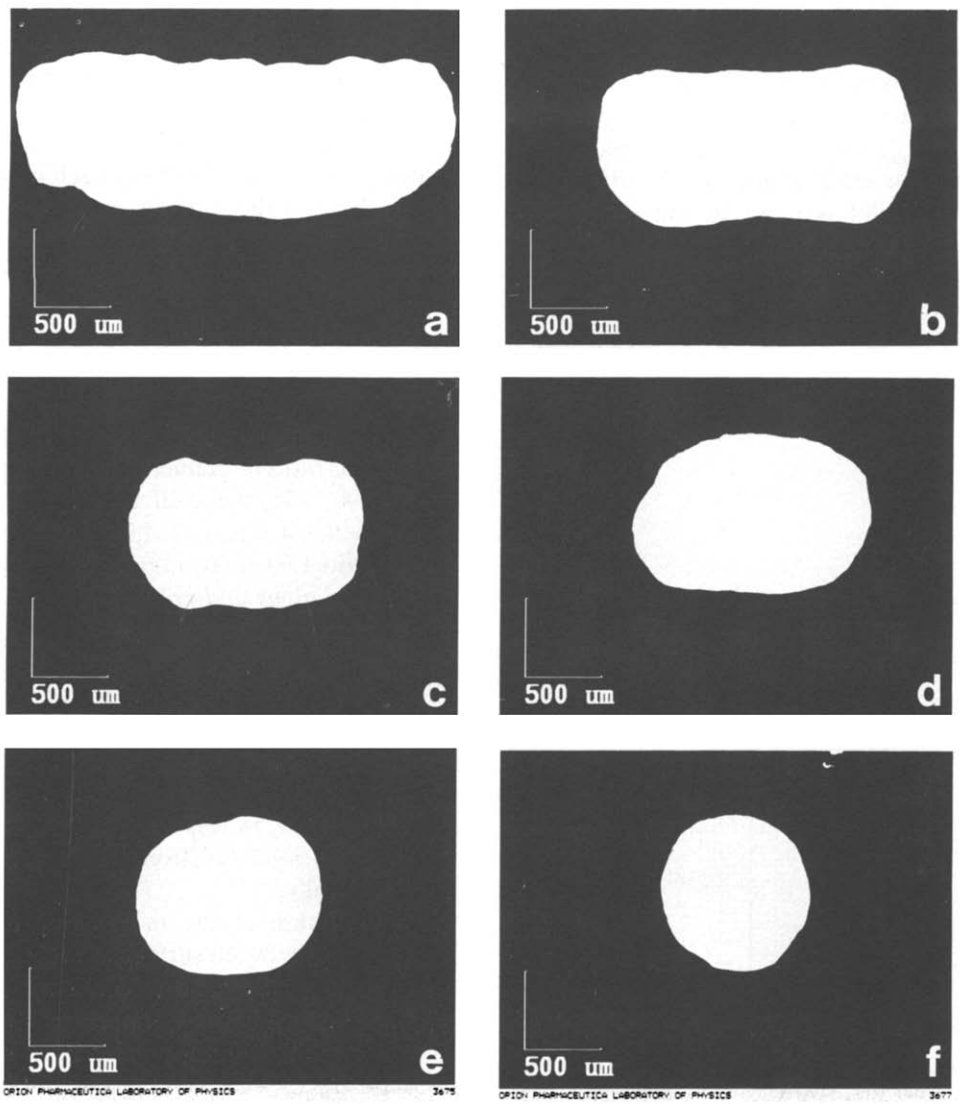

Fig. 2. Pellets representing shape groups I–VI (panels a–f, respectively).

$(4\pi 0.50^2/(4/3)\pi 0.50^3 = 6.00)$. In the case of the roundest pellet F, the ratio was 6.17, differing only 2.8% from the ideal value.

Size parameters as a function of number of pellets measured

When evaluating the size of pellets in a sample or batch, it is of the utmost importance to know how many pellets are needed to give reliable and representative mean size values. For this purpose the mean values of five measured size parameters are presented in Fig. 3A–E. The development of mean values of size parameters as a function of number of pellets has been calculated using 25 pellet intervals up to 800 pellets. Photographs of pellets representing these samples are shown in Fig. 2.

In the case of minimum diameter, the values varied within quite a narrow range: all mean values were between 0.80 and 0.95 μm (Fig. 3A). The mean values of the roundest pellets (F) remained stable after 300 pellets, while in other batches 600 or more pellets were needed.

The behaviour of mean values of pellet batches of maximum diameter, perimeters and two-dimensional area was very similar (Fig. 3B–E). The

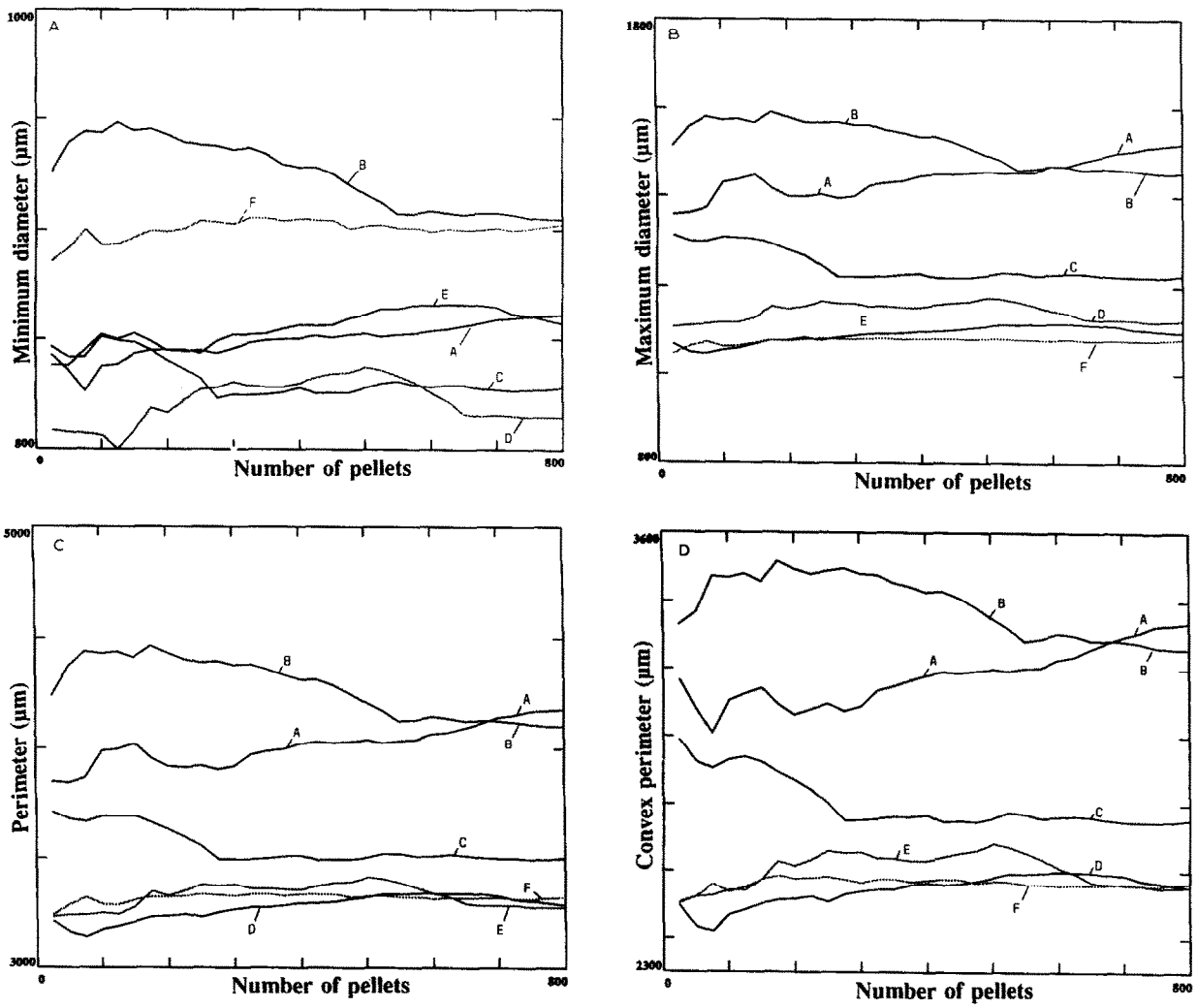

Fig. 3. The development of mean values of size parameters (batches A–F) as a function of number of pellets: (A) d_{min}, (B) d_{max}, (C) perim, (D) cperim, (E) two-dimensional area.

TABLE 1

Measured, derived and geometric diameter, three-dimensional area and volume parameters for the six pellets

	A	B	C	D	E	F
Diameters (mm)						
d_{min}	1.06	1.03	0.96	1.02	1.00	0.97
d_{max}	2.89	2.06	1.54	1.57	1.24	1.03
d_{ave}	1.97	1.55	1.25	1.30	1.12	1.00
d_{perim}	2.31	1.72	1.37	1.36	1.19	1.04
d_{cperim}	1.76	1.37	1.07	1.06	0.90	0.77
d_{area}	1.80	1.53	1.26	1.28	1.13	0.98
$d_{min,geom}$	0.97	0.91	0.86	0.98	0.93	0.96
$d_{max,geom}$	2.89	2.06	1.54	1.58	1.22	1.00
$d_{ave,geom}$	1.93	1.48	1.21	1.28	1.08	0.98
Surface areas (mm^2)						
$A_{d_{min}}$	3.52	3.33	2.87	3.25	3.13	2.94
$A_{d_{max}}$	26.17	13.36	7.47	7.76	4.85	3.33
$A_{d_{ave}}$	12.22	7.51	4.90	5.27	3.94	3.14
$A_{d_{perim}}$	16.78	9.28	5.92	5.84	4.44	3.43
$A_{d_{cperim}}$	9.74	5.88	3.60	3.52	2.54	1.87
$A_{d_{area}}$	10.20	7.34	5.00	5.15	3.98	3.02
A_{geom}	8.76	6.31	4.30	4.45	3.42	2.96
Volumes (mm^3)						
$V_{d_{min}}$	0.62	0.57	0.46	0.55	0.52	0.46
$V_{d_{max}}$	12.59	4.59	1.92	2.03	1.00	0.57
$V_{d_{ave}}$	4.02	1.94	1.02	1.14	0.74	0.52
$V_{d_{perim}}$	6.46	2.66	1.36	1.33	0.88	0.60
$V_{d_{cperim}}$	2.86	1.34	0.64	0.62	0.38	0.24
$V_{d_{area}}$	3.06	1.87	1.05	1.10	0.75	0.49
V_{geom}	2.13	1.56	0.99	1.05	0.80	0.48

Batch codes A–F refer to Figs 2 and 3.

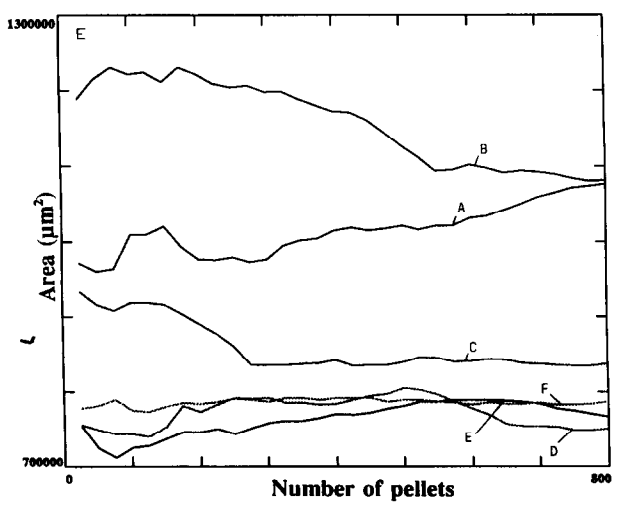

Fig. 3 (continued).

behaviour of the most elongated pellets (A and B) was very unstable – for this kind of heterogeneous batches the appropriate number of pellets to be measured would be 800. In the case of less elongated pellets, less might be enough. Only in the case of the roundest pellets was stability already achieved after 200 pellets.

Effect of process variables on the size and size distribution of pellets

The only exact way to describe distributions is to represent them. As an example, d_{max} distributions of batches A–F are presented in Fig. 4. Differences between batches can be observed clearly: distributions A and B were wide – widths 1.19 and 1.07 mm, respectively – indicating heterogeneous batches, while the distribution of a homogeneous batch F was narrow, 0.43 mm, and sharp.

However, the comparison of 66 pellet batches by studying the shape of 18 different size parameter distributions is a very time-consuming method. Therefore, the effect of process variables on the size of pellets was studied by comparing important distribution characteristics of size distributions, i.e., median (50%), width (90–10%) and span ((90–10%/50%)100).

On the basis of preliminary analysis of variance studies (Systat V5.0, Systat Inc., U.S.A.), only four variables were found to affect significantly the size of pellets. Those variables and levels studied are presented in Table 2, which acts as a key to subsequent tables (Tables 3–5).

Diameters The median d_{min} values of all batches were quite similar, varying only between 0.84 and 0.95 μm (Table 3). The median d_{max} values, instead, ranged from 0.98 to 1.57 mm. The difference between these two parameters can also be seen in Fig. 5. In the case of d_{max}, every second batch has clearly higher median values, indicating a powerful effect of the speed of the friction plate on the size of pellets; the effect was also similar on the widths of the distributions. An interesting correlation between the widths of the d_{min} distribution and d_{max} median values was found – with increasing median d_{max} value the width of d_{min} distribution decreased. It is possible that when the granulation and extrusion pro-

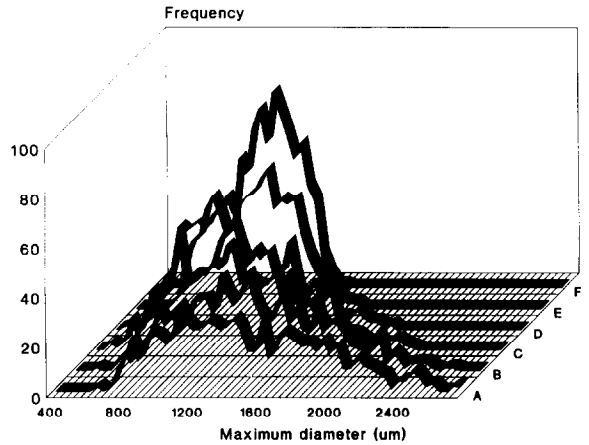

Fig. 4. d_{max} distributions of pellet batches A–F.

cesses compact the mass more, the extrudate becomes stiffer, less mouldable and less breakable, and thus the dmin values of pellets become more homogeneous.

The derived parameters d_{ave} and d_{area} gave quite similar values for distribution characteristics, but they did not include important information about pellet shape – the oblongation. The

TABLE 2

Levels of most significant process variables – size of the granule outlet (G3), load (S1), residence time (S2) and speed of the friction plate (S3)

Expt no.	G3 (mm) 8 (−) 16 (+)	S1 (g) 100 (−) 400 (+)	S2 (min) 2 (−) 8 (+)	S3 (rpm) 500 (−) 900 (+)
1 (A)	−	−	−	−
2	−	−	−	+
3	−	−	+	−
4	−	−	+	+
5	−	+	−	−
6	−	+	−	+
7	−	+	+	−
8	−	+	+	+
9	+	−	−	−
10	+	−	−	+
11	+	−	+	−
12	+	−	+	+
13	+	+	−	−
14	+	+	−	+
15	+	+	+	−
16	+	+	+	+
48 (F)	+	+	+	+

d_{perim} parameter was clearly greater than d_{cperim}, and closest to the d_{max}.

The difference between heterogeneous batch A and homogeneous batch F (Expts 1 and 48, respectively) is clear: in the case of the homogeneous batch median values of different diameter parameters are quite similar, and both widths and spans of distributions are significantly lower than in the case of batch A.

The reproducibility of the process was acceptable, differences in median values between four parallel tests being less than 8%.

According to earlier studies (Rowe, 1985; Baert et al., 1992), the size distribution of a pellet batch can be considered to be acceptable and narrow if 90% of the pellets show a particle size between 0.7 and 1.4 μm (sieve analysis). When the d_{max} distributions of the present study (Table 3) are compared with the claim mentioned above, only two batches (Expts 16 and 48) would be acceptable. Instead, in an earlier study (Hellén et al., 1993a), where the extruder variables were evaluated using the same formulation and spheroniser adjustments as in the present study, almost all batches would have been acceptable. Irrespective of the size measurement method used, these results clearly show the importance of optimisation of the spheronisation stage when a sensitive formulation is used.

Surface areas and volumes The surface area and volume are second- and third-order functions of a diameter, respectively, and consequently even more sensitive. Hence, the effect of the speed of the friction plate can also clearly be seen from the surface area (Table 4) and the volume (Table 5) values – in most cases the size parameter values, as well as those of width and span, decrease with increasing speed. Here too, d_{min} is an exception.

It seems obvious that in both cases parameters derived from d_{min} or d_{cper} underestimate, and parameters derived from d_{max} overestimate the size of a pellet. When the surface area or the volume of a spherical or almost spherical pellet is determined, parameters derived via d_{ave} or d_{area} should be used. In future, the suitability of these parameters in determination of, e.g., density of pellets, will be studied.

TABLE 3

Measured and derived diameter parameters of the pellets in μm

Expt no	d_{min}			d_{max}			d_{ave}			d_{perim}			d_{cperim}			d_{area}		
	m	w	s	m	w	s	m	w	s	m	w	s	m	w	s	m	w	s
1 (A)	873	183	21	1461	1185	81	1166	663	56	1307	840	64	1026	806	78	1145	590	51
2	848	292	34	1072	787	73	963	525	54	1022	614	60	787	545	69	950	508	53
3	899	155	17	1500	1123	74	1204	621	51	1345	806	59	1069	740	69	1187	550	46
4	877	261	29	1173	734	62	1026	501	48	1101	591	53	850	542	63	1022	488	47
5	874	148	16	1570	1237	78	1221	671	55	1369	854	62	1098	804	73	1192	573	48
6	894	281	31	1221	762	62	1061	512	48	1141	606	53	888	531	59	1054	502	47
7	844	217	25	1344	1080	80	1094	642	58	1220	814	66	960	735	76	1083	580	53
8	953	175	18	1273	513	40	1114	330	29	1206	411	34	950	402	42	1117	334	29
10	816	387	47	978	748	76	904	556	61	956	626	65	734	555	75	897	554	61
11	870	234	26	1321	1104	83	1092	657	60	1204	814	67	932	730	78	1089	594	54
12	874	294	33	1125	761	67	1006	521	51	1075	616	57	826	535	64	1004	510	50
13	850	181	21	1339	936	69	1094	546	49	1214	701	57	941	659	70	1086	498	45
14	923	338	36	1163	728	62	1048	531	50	1113	614	55	878	553	63	1034	524	50
15	882	240	27	1315	1036	78	1096	622	56	1209	800	66	941	749	79	1090	585	53
16	899	367	40	1083	620	57	989	485	49	1049	562	53	817	496	60	986	498	50
48 (F)	910	292	32	1087	430	39	999	344	34	1062	396	37	812	363	45	999	355	35

Experiment numbers refer to Table 2 (m, median; w, 90–10%; s, ((90–10%)/50%)×100).

TABLE 4

Derived surface areas of the pellets in mm^2

Expt no	$A_{d_{min}}$			$A_{d_{max}}$			$A_{d_{ave}}$			$A_{d\text{perim}}$			$A_{d\text{cperim}}$			$A_{d\text{area}}$		
	m	w	s	m	w	s	m	w	s	m	w	s	m	w	s	m	w	s
1 (A)	2.40	1.00	41	6.72	11.56	172	4.28	5.00	117	5.36	7.08	132	3.32	5.52	167	4.12	4.24	103
2	2.28	1.44	64	3.60	5.76	160	2.92	3.20	110	3.28	4.08	124	1.96	2.88	147	2.84	3.60	108
3	2.56	0.88	34	7.08	11.12	157	4.56	4.80	104	5.68	6.96	122	3.60	5.12	143	4.44	4.08	92
4	2.40	1.36	56	4.32	5.52	127	3.32	3.16	96	3.80	4.08	107	2.28	2.96	131	3.28	3.08	94
5	2.40	0.80	33	7.76	12.72	164	4.68	5.28	112	5.88	7.48	127	3.80	5.72	151	4.44	4.24	95
6	2.52	1.48	58	4.68	5.76	123	3.52	3.28	92	4.08	4.24	103	2.48	2.92	118	3.48	3.20	91
7	2.24	1.12	49	5.68	9.48	167	3.76	4.44	118	4.68	6.32	135	2.88	4.56	158	3.68	3.88	105
8	2.88	1.04	36	5.08	4.04	80	3.88	2.28	59	4.56	3.08	67	2.84	2.36	84	3.92	2.28	59
9	2.64	1.12	43	7.04	11.60	165	4.60	5.12	110	5.60	7.12	127	3.44	5.44	157	4.44	4.36	98
10	2.08	1.84	88	3.00	4.96	165	2.56	3.16	122	2.88	3.88	135	1.68	2.64	157	2.52	3.16	125
11	2.36	1.24	52	5.48	9.96	181	3.76	4.68	124	4.56	6.44	142	2.72	4.56	167	3.72	4.12	110
12	2.40	1.52	63	3.96	5.60	140	3.16	3.24	102	3.64	4.16	115	2.16	2.84	133	3.16	3.16	100
13	2.28	0.96	42	5.64	8.24	147	3.76	3.84	102	4.64	5.48	119	2.80	4.08	147	3.68	3.40	91
14	2.68	1.80	68	4.24	5.48	129	3.44	3.40	98	3.88	4.28	10	2.44	3.08	127	3.36	3.32	99
15	2.44	1.28	52	5.44	9.16	168	3.76	4.36	116	4.60	6.28	137	2.80	4.68	168	3.72	4.00	107
16	2.56	2.00	78	3.68	4.24	116	3.08	2.96	96	3.44	3.72	108	2.08	2.56	123	3.04	3.04	100
48 (F)	2.60	1.64	63	3.72	2.92	79	3.12	2.12	68	3.52	2.64	74	2.08	1.88	91	3.12	2.20	70

Experiment numbers refer to Table 2 (m, median; w, 90–10%; s, ((90–10%)/50%)×100).

TABLE 5

Derived volumes of the pellets in mm^3

Expt no	$V_{d_{min}}$			$V_{d_{max}}$			$V_{d_{ave}}$			V_{dperim}			V_{dperim}			V_{darea}		
	m	w	s	m	w	s	m	w	s	m	w	s	m	w	s	m	w	s
1 (A)	0.35	0.21	61	1.63	4.71	288	0.83	1.54	186	1.17	2.44	209	0.57	1.57	278	0.79	1.24	157
2	0.32	0.29	91	0.65	1.75	271	0.47	0.80	171	0.56	1.10	198	0.26	0.62	243	0.45	0.75	167
3	0.38	0.19	51	1.77	4.58	260	0.91	1.51	165	1.27	2.45	193	0.64	1.47	230	0.87	1.22	140
4	0.35	0.28	80	0.85	1.70	201	0.57	0.81	144	0.70	1.14	163	0.32	0.66	207	0.56	0.78	140
5	0.35	0.17	50	2.03	5.44	268	0.95	1.70	178	1.34	2.69	200	0.69	1.68	243	0.89	1.27	143
6	0.37	0.31	82	0.95	1.80	189	0.63	0.85	136	0.78	1.20	155	0.37	0.65	178	0.61	0.82	134
7	0.31	0.22	71	1.27	3.48	274	0.68	1.26	184	0.95	2.02	213	0.46	1.19	256	0.67	1.06	159
8	0.45	0.24	53	1.08	1.29	120	0.72	0.62	86	0.92	0.92	100	0.45	0.56	126	0.73	0.63	87
9	0.40	0.25	63	1.76	4.73	269	0.92	1.60	173	1.25	2.48	199	0.60	1.56	257	0.88	1.30	147
10	0.28	0.35	124	0.49	1.37	280	0.39	0.74	191	0.46	0.98	215	0.21	0.53	255	0.38	0.74	195
11	0.34	0.26	76	1.21	3.74	310	0.68	1.37	201	0.91	2.11	231	0.42	1.19	281	0.68	1.16	171
12	0.35	0.32	90	0.75	1.69	227	0.53	0.82	155	0.65	1.16	178	0.30	0.63	212	0.53	0.79	150
13	0.32	0.20	61	1.26	3.01	239	0.69	1.10	161	0.94	1.75	187	0.44	1.04	238	0.67	0.93	139
14	0.41	0.39	94	0.82	1.69	206	0.60	0.90	149	0.72	1.22	169	0.35	0.70	198	0.58	0.86	149
15	0.36	0.27	75	1.19	3.36	282	0.69	1.25	181	0.93	2.02	218	0.44	1.22	279	0.68	1.11	164
16	0.38	0.43	114	0.67	1.20	180	0.51	0.74	146	0.60	1.00	166	0.29	0.55	192	0.50	0.76	152
48 (F)	0.40	0.37	95	0.67	0.80	119	0.52	0.53	102	0.63	0.71	113	0.28	0.39	140	0.52	0.55	106

Experiment numbers refer to Table 2 (m, median; w, 90–10%; s, ((90–10%)/50%)×100).

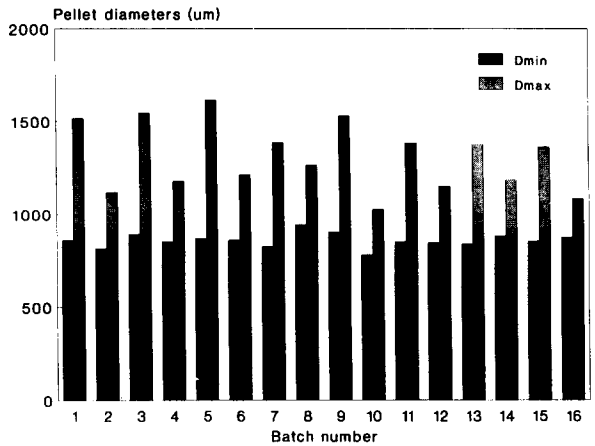

Fig. 5. d_{min} and d_{max} median values of pellet batches 1–16 (Table 3).

Statistical analysis

Interactions between process variables and size distribution characteristics were analyzed using the analysis of variance (ANOVA) and the Pearson correlation (Systat 5.0 V, Systat Inc., U.S.A.). Preliminary analyses showed that neither the amount of water used as a granulation liquid (G1) nor the speed of powder additon (G2) during granulation could explain any changes in the size of pellets. The amount of water, 35 or 38%, was selected on the basis of preliminary studies so that the production of dust and large agglomerates was avoided. Obviously, the formulation used was so insensitive to changes in the amount of water that no significant effect on size parameters studied was observed.

The effect of size of the granule outlet (G3) and speed of the friction plate (S3) was most significant on all size parameters (Table 6). In both cases the correlation was negative, i.e., when a larger granule outlet (consequently lighter kneading during granulation), and a higher speed of the friction plate were used, the pellets were smaller. Evidently, the granulator is able to knead the wet mass during instant granulation so powerfully – due to the small volume of the mixing chamber and also the high speed of the turbine wheel – that high energy input is needed to deform the wet extrudate. A greater load of spheroniser (S1), by increasing the interparticular friction, and a longer residence time (S2) reduced the size of pellets – this effect was most significant on the 90% fractile values.

Hasznos et al. (1992) have found that the speed of the spheroniser and the residence time had a significant effect on the pellet mean diameter. However, the direction of the changes was opposite compared to that of the present study: the mean diameter increased when the levels of factors increased. Differences between the results of these two studies may be due to differences in either the preparation methods prior to spheronisation, plastic properties of the wet mass or the particle size characterisation method used.

In general, the extrusion operation is the major contributing factor in the final particle size of pellets (O'Connor and Schwartz, 1989). The diameter of the screen determines one dimension of the pellet very strictly. When the diameter of

TABLE 6

Analysis of variance and Pearson correlation

	G3	S1	S2	S3
d_{min}				
10%	[a]	–	–	[a]
50%	–	–	–	–
90%	[b]	–	–	[c]
d_{max}				
10%	[a]	–	[c]	[a] (–)
50%	[a]	[c]	[b]	[a] (–)
90%	[a]	[a]	[a]	[a] (–)
perim				
10%	[a] (–)	–	–	[a] (–)
50%	[a] (–)	[c]	[b]	[a] (–)
90%	[a] (–)	[a] (–)	[a]	[a] (–)
cperim				
10%	[a] (–)	–	–	[a] (–)
50%	[a] (–)	–	[c]	[a] (–)
90%	[a] (–)	[a]	[a] (–)	[a] (–)
area				
10%	[a] (–)	–	–	[a] (–)
50%	[a] (–)	[c]	[c]	[a] (–)
90%	[b] (–)	[a] (–)	[a] (–)	[a] (–)

The effect of significant process variable of the granulator (size of the granule outlet (G3)), and the effect of the variables of the spheroniser (load (S1), residence time (S2) and speed of the friction plate (S3)) on the size distribution characteristics of pellets are indicated.

[a] $p < 0.001$; [b] $p < 0.01$; [c] $p < 0.05$; –, no effect; (+), positive correlation; (–), negative correlation.

the screen is kept constant, the density of granules – i.e., the effect of the size of the granule outlet – and intensity of spheronisation stage – i.e., load, time and speed – apparently determine most prominently how the extrudate will be cut and rounded. Using the formulation and equipment studied, acceptable pellets with narrow size distribution and good reproducibility can be produced when larger granule outlet, larger load, longer residence time and higher speed of the friction plate are used.

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References

Allen, T., Particle size, shape and distribution. In Scarlett, B. (Ed.), *Particle Size Measurement,* Chapman and Hall, London, 1990, pp. 124–191.

Baert, L., Fanara, J., Remon, J.P. and Massart, D., Correlation of extrusion forces, raw materials and sphere characteristics. *J. Pharm. Pharmacol.,* 44 (1992).

Conine, J.W. and Hadley, H.R., Small solid pharmaceutical spheres. *Drug Cosm. Ind.,* 90 (1970) 38–41.

Ghebre-Sellassie, I., Pellets: A general overview. *Pharmaceutical Pelletization Technology,* Dekker, New York, 1989, pp. 1–13.

Hasznos, L., Langer, I. and Gyarmathy, M., Some factors influencing pellet characteristics made by an extrusion/spheronisation process: I. Effects on size characteristics and moisture content decrease of pellets. *Drug Dev. Ind. Pharm.,* 18 (1992) 409–437.

Hellén, L., Yliruusi, J., Muttonen, E. and Kristoffersson, E., Process variables of the radial screen extruder: II. Size and size distribution of pellets. *Pharm. Techn. Int.,* 5 (1993a) 44–53.

Hellén, L., Yliruusi, J., Merkku, P. and Kristoffersson, E., Process variables of the radial screen extruder: Part III - shape, surface and flow properties of pellets. *Pharm. Techn. Int.,* 5 (1993b) 38–48.

Hellén, L., Yliruusi, J., Merkku, P. and Kristoffersson, E., Process variables of instant granulator and spheroniser: I. Physical properties of granules, extrudate and pellets. *Int. J. Pharm.,* 96 (1993c) 197–204.

Iley, W.J., Effect of particle size and porosity on particle film coatings. *Powder Technol.,* 65 (1991) 441–445.

Mehta A.M., Evaluation and characterization of pellets. In Ghebre-Sellassie, I. (Ed.), *Pharmaceutical Pelletization Technology,* Dekker, New York, 1989, pp. 241–265.

O'Connor, R.E. and Schwartz, J.B., Extrusion and spheronisation technology. In Ghebre-Sellassie, I. (Ed.), *Pharmaceutical Pelletization Technology,* Dekker, New York, 1989, pp. 187–216.

Reynolds, A.D., A new technique for the production of spherical particles. *Manuf. Chem.,* June (1970) 39–43.

Rowe, R.C., Spheronization: a novel pill-making process? *Pharm. Int.,* May (1985) 119–123.

Schæfer, T., Equipment for wet granulation. *Acta Pharm. Suec.,* 25 (1988) 205–228.

Wesdyk, R., Joshi, Y.M., Jain, N.B., Morris, K. and Newman, A., The effect of size and mass on the film thickness of beads coated in fluidized bed equipment. *Int. J. Pharm.,* 65 (1990) 69–76.