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Process variables of instant granulator and spheroniser: I. Physical properties of granules, extrudate and pellets

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Summary

The influence of process variables of a continuously working instant Nica granulator, and those of a spheroniser on the stability of moisture content during the process, the surface morphology, friability, packing and flow properties of pellets was evaluated. A complete six-factor, two-level study design was used. The moisture content of granules and extrudate corresponded well to the amount of water used as a granulation liquid. Hence, until the spheronisation stage, the stability of moisture content was maintained. During spheronisation, the moisture content decreased due to the effect of residence time and friction plate speed. The surface morphology of pellets was dependent on the amount of water used; with a higher water amount the surface was smoother. The process variables of the spheroniser explained most significantly the changes in packing properties of pellets: the bulk and tapped density increased with increasing load, time and speed in the spheroniser.

Introduction

Extrusion/spheronisation is one of the most widely used pelletization techniques in the pharmaceutical industry. This process consists of several stages: dry blending, wet granulation of the mass, extrusion of the moist mass, spheronisation of the extrudate, and drying and sieving of the pellets.

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Granulation of the mass for extrusion and spheronisation is mostly performed using batch mixers, e.g., planetary or high shear granulators (Schæfer, 1988; Titley, 1988). Another type of mixer used is the continuously working, instantaneous one. With the continuous mixer, the granulation and extrusion work can be synchronised to achieve continuously a homogeneous product for the spheronisation process.

The effect of the radial screen extruder, attached to a continuous instant granulator, on the extrudate and pellet properties has been studied earlier (Hellén, 1992, 1993a,b). The objective of this study was to examine how the process vari-

ables of a continuously working instant Nica granulator and those of a spheroniser affect the moisture content of granules, extrudate and pellets, the surface structure of extrudate and pellets, and friability, packing and flow properties of pellets.

Materials and Methods

Materials

The starting materials used were of Ph.Eur. grade, and contained mannitol (Merck, Germany), microcrystalline cellulose (Emcocel 50M, Edward Mendell Co., U.S.A.) and caffeine (Boehringer Ingelheim, Germany). Distilled water was used as the granulation liquid. The composition of dry substances was as follows: mannitol, 75%; microcrystalline cellulose, 20%; caffeine, 5%.

The amount of distilled water added was 35 or 38% on the basis of dry weight, i.e., 25.9 or 27.5% of the wetted mass, respectively.

Equipment

The Nica pelletising equipment consisted of a granulator, an extruder and a spheroniser. The granulator (Nica M6L, Nica System AB Mölndal, Sweden) works continuously, and mixes the solid and liquid components together instantaneously. The mixing system is based on a high speed turbine in which the powder and liquid phase meet. The speed of the turbine wheel is 2800 rpm (23 m/s at the periphery). The speeds of both the powder feeder and the liquid pump can be adjusted separately and varied steplessly in the range of 35–200 rpm. The load of the mixing chamber can be controlled by altering either the size of the granule outlet area or the powder and liquid input rate (Appelgren, 1985; Lindberg, 1988; Hellén et al., 1992).

The extruder (Nica E 140) is a radial screen extruder in which the feeder and the agitator rotate in opposite directions, pressing the material through the vertical screen.

The spheroniser (Nica S320) consists of a stationary vertical cylinder which has at the base a friction plate (diameter 32 cm) with a cross-hatched friction pattern and a rotation speed of 200–1000 rpm. A special feature of this spheroniser is that is has a lip around the periphery of the disc, which should eliminate the milling effect of the plate edges.

Experimental design

The experimental design used was a six-factor design, each factor being studied at two levels. The process variables of the granulator (G1–G3) were the amount of water, the speed of powder addition and the size of granule outlet. The process variables of the spheroniser (S1–S3) were the load of the spheroniser, the residence time and the speed of the friction plate. The levels of the variables used are shown in Table 1.

The reproducibility of the process was tested by repeating two tests: Expts 10 and 38 were repeated (Expts 65 and 66, respectively).

Preparation of pellets

The dry substances were mixed in a high shear mixer (Fielder PMA 25, J.K. Fielder Ltd, Eastleigh, U.K.). The mass was granulated in the Nica granulator. The speed of the powder feeder was 1533 g/min, corresponding to 35 rpm, or 2777 g/min, corresponding to 65 rpm. The amount of water added was 25.9 or 27.5% (i.e., 35 or 38% on the basis of dry weight, respectively). Measured from the lower side of the outlet, the size of the granule outlet was 8 or 16 mm.

The moist mass was extruded immediately after the granulation. In this study the set-ups of the extruder were kept constant in order to emphasise the effect of the granulator variables.

TABLE 1

Independent process variables of the granulator (G) and the spheroniser (S) and the levels studied

Variable	Level	
	−	+
(G1) Amount of water (%)	25.9	27.5
(G2) Speed of powder addition (rpm)	35	65
(G3) Size of granule outlet (mm)	8	16
(S1) Load of the spheroniser (g)	100	400
(S2) Residence time (min)	2	8
(S3) Speed of friction plate (rpm)	500	900

Thus, throuhgout the study, the 1.00 mm screen was used where the diameters of the dies were 1 mm and the number of dies per unit area was 30 cm^{-2}. The speed of the feeder was 45 rpm and that of the agitator 35 rpm. The effects of the variables of the extruder on extrudate and pellet properties have been studied earlier (Hellén et al., 1992, 1993a,b).

The wet extrudate was spheronised. The load of the spheroniser was 100 or 400 g of extrudate, the speed of the friction plate was 500 or 900 rpm, i.e., 8 or 15 m/s in the periphery of the plate, and the residence time was 2 or 8 min.

The granules, extrudate and pellets were dried on trays as a monolayer at room temperature (21–25°C) and at a relative humidity of 48–65% until the moisture content was $< 2\%$, i.e., for 72 h.

Analytical methods

The moisture content of granules, extrudate and pellets was measured immediately after each process stage by drying 2 g of the material in an infrared dryer at 60°C (Sartorius Thermo Control YTC 01 L, Germany) until the change in weight was less than 0.1% in 50 s.

The length of extrudate was studied by taking an instant photograph (Polaroid Image pro, Polaroid, St. Albans, U.K.) during the extrusion stage. The photograph was always taken at the same phase of extrusion, 20 s after the beginning of the process.

The visual shape investigation of pellets was performed by classifying the pellet batches into six shape groups, I–VI, so that the batch which had the roundest pellets represented group VI.

The surface structure of pellets was studied by using scanning electron microscopy (Jeol JSM-840A, Japanese Electron Optical Ltd, Tokyo, Japan). For this purpose, samples of each batch of pellets were coated with gold in an argon atmosphere by an ion sputter coater (SD004, Baltzers Union, Baltzers, Liechtenstein) before a photograph was taken.

The friability of pellets was studied using a Roche-type friabilator with an abrasion wheel. The amount of pellets used in the test was 5 g; the size fraction used was > 0.25 mm. The abrasion was enhanced using 10 g of glass beads (diameter 4 mm). After rotation for 200 revolutions, the percent weight loss was determined (Millili and Schwartz, 1990).

The bulk density of pellets was determined by weighing 100 ml of pellets poured into a graduated cylinder. The tapped density was measured by tapping 100 ml of pellets 1000 times (Erweka SVM, Germany). Both tests were made in triplicate. The Hausner ratio (Hausner, 1967) was calculated.

The flow time of pellets was measured by an automated flowability tester (Pharmatest type PTG, Germany) using an 8 mm orifice and 100 ml of pellets.

Statistical analyses, i.e., analysis of variance and Pearson correlation, were performed using the MS/DOS version of Systat 5.0 (Systat Inc., U.S.A.).

Results and Discussion

Moisture content of granules, extrudate and pellets

In the pelletization process water acts as a glidant during the extrusion stage (O'Connor and Schwartz, 1989), and it is also related to the plasticity of pellets during spheronisation. To be able to control the pelletization process, the changes in moisture content during the process must be known.

TABLE 2

Moisture content of granules and extrudate

Variable levels			Moisture content (%) ($x \pm$ S.D., $n = 8$)			
G1	G2	G3	Granules		Extrudate	
−	−	−	25.6	0.5	24.9	0.4
−	−	+	25.3	0.5	25.4	0.1
−	+	−	25.9	0.5	25.8	0.2
−	+	+	26.2	1.0	26.2	0.2
+	−	−	27.0	0.3	26.6	0.4
+	−	+	26.8	0.5	27.0	0.3
+	+	−	27.1	0.6	27.2	0.4
+	+	+	28.0	0.9	27.8	0.2

G1, amount of water; G2, speed of powder addition; G3, size of granule outlet.

The moisture content of granules and extrudate corresponded well to the amount of water used as granulation liquid – no statistical differences between the theoretical amount of water (G1) and the moisture content of granules and extrudate were found (Table 2). Neither the rate of powder addition (G2) nor the size of the granule outlet (G3) affected the moisture content of granules or extrudate significantly. In an earlier study, Hellén et al. (1992) found that the variables of the radial screen extruder – thickness of the screen, speed of the feeder and speed of the agitator – did not affect the moisture content of the extrudate. Since moisture evaporation and also the heat production during the granulation and the extrusion stages of the process have been

TABLE 3

Physical properties of pellets

Expt no	Factor levels						MC (%)	dMC (%)	VSG	Friability (%) ($n = 3$)		Densities (g/ml) ($n = 3$) [a]		Hausner ratio	Flow time (s/100 ml) ($n = 3$) [b]
	G1	G2	G3	S1	S2	S3				$x \pm$	SD	Bulk	Tapped		
1	–	–	–	–	–	–	24.4	0.7	I	2.6	0.9	0.49	0.55	1.12	15.5
2	–	–	–	–	–	+	22.5	1.9	IV	2.5	0.6	0.56	0.62	1.11	14.1
3	–	–	–	–	+	–	22.8	2.7	II	2.7	0.9	0.54	0.61	1.13	15.2
4	–	–	–	–	+	+	17.2	7.3	IV	0.7	0.1	0.63	0.70	1.11	14.3
5	–	–	–	+	–	–	24.2	0.5	I	1.2	0.4	0.52	0.57	1.10	16.9
6	–	–	–	+	–	+	23.9	0.9	IV	0.9	0.7	0.60	0.67	1.12	14.8
7	–	–	–	+	+	–	24.0	1.0	II	1.2	0.2	0.56	0.61	1.09	16.3
8	–	–	–	+	+	+	21.1	4.0	V	1.5	0.7	0.69	0.76	1.10	14.3
9	–	–	+	–	–	–	24.8	0.8	I	2.1	0.1	0.46	0.52	1.13	16.1
10	–	–	+	–	–	+	23.1	2.3	IV	2.0	0.9	0.56	0.62	1.11	13.3
11	–	–	+	–	+	–	21.1	4.3	II	1.6	0.7	0.55	0.60	1.09	15.6
12	–	–	+	–	+	+	20.4	5.0	III	0.9	0.8	0.64	0.69	1.08	13.6
13	–	–	+	+	–	–	24.2	1.2	II	1.1	0.3	0.55	0.61	1.11	16.8
14	–	–	+	+	–	+	24.3	1.0	III	0.9	0.2	0.61	0.65	1.07	13.5
15	–	–	+	+	+	–	24.1	1.2	III	1.1	0.3	0.55	0.61	1.11	15.7
16	–	–	+	+	+	+	21.8	3.5	V	1.6	0.9	0.67	0.74	1.10	13.9
17	–	+	–	–	–	–	25.5	0.4	I	1.9	0.6	0.47	0.53	1.13	16.4
18	–	+	–	–	–	+	24.0	1.3	III	0.9	0.5	0.55	0.61	1.11	14.7
19	–	+	–	–	+	–	21.9	3.8	I	0.6	0.2	0.54	0.61	1.13	17.1
20	–	+	–	–	+	+	17.4	8.3	IV	1.9	0.5	0.63	0.68	1.08	14.5
21	–	+	–	+	–	–	25.6	0.2	I	1.1	0.9	0.53	0.58	1.09	18.0
22	–	+	–	+	–	+	24.3	1.5	III	2.5	0.9	0.61	0.67	1.10	15.9
23	–	+	–	+	+	–	24.2	1.8	II	0.3	0.3	0.56	0.62	1.11	16.9
24	–	+	–	+	+	+	23.1	3.0	IV	0.9	0.7	0.67	0.77	1.15	15.1
25	–	+	+	–	–	–	25.0	1.3	II	2.5	0.5	0.49	0.55	1.12	16.3
26	–	+	+	–	–	+	24.9	1.3	III	1.3	0.7	0.57	0.63	1.11	14.1
27	–	+	+	–	+	–	23.3	2.7	II	1.3	1.4	0.53	0.58	1.09	16.1
28	–	+	+	–	+	+	20.9	5.3	III	0.8	0.5	0.63	0.68	1.08	14.0
29	–	+	+	+	–	–	25.5	0.5	II	2.5	1.3	0.49	0.55	1.12	16.5
30	–	+	+	+	–	+	25.3	0.9	IV	0.6	0.2	0.57	0.64	1.12	15.2
31	–	+	+	+	+	–	25.0	1.4	II	0.7	0.1	0.55	0.62	1.13	16.4
32	–	+	+	+	+	+	23.9	2.5	V	1.2	0.7	0.68	0.74	1.09	14.0
65	–	–	+	–	–	+	23.5	2.5	IV	1.8	0.8	0.56	0.62	1.11	13.4

G1, amount of water; G2, speed of powder addition; G3, size of granule outlet; S1, load of the spheroniser; S2, residence time; S3, speed of friction plate; MC, moisture content of pellets; dMC, change of moisture content during spheronisation; VSG, visual shape group I–VI (VI = roundest). [a] SD < 0.01; [b] SD < 0.1.

found to be insignificant, it can be concluded that the Nica granulator and extruder caused only a small internal friction force in the mass.

During the spheronisation stage the moisture content decreased; the loss of moisture content varied between 0.2 and 8.3%. The reproducibility of the process was very good – the differences between parallel tests were only 1.7%. The moisture content of pellets produced using a lower amount of water, and the decrease in moisture content during the process are presented in Table 3. The decrease in moisture content during the spheronisation process of experiments 1–8 has also visualised in Fig. 1. The effect of the residence time (S2) and friction plate speed (S3) on the moisture content of pellets was significant ($p < 0.01$): with longer residence time and faster speed the evaporation of moisture was maximal. This effect was less prominent when a greater load in spheroniser (S1) was used. Similar results have been obtained earlier by Hasznos et al. (1990) irrespective of the differences in the formulation and equipment used.

It can be concluded that the moisture content of granules corresponded to the amount of water used as granulation liquid. Until the spheronisation stage stability in moisture content was maintained. During spheronisation the moisture content decreased, but also remained adequate for formation of spherical pellets.

Length of extrudate

The macrostructure and quality of the extrudate can readily be studied by observing the length of the produced extrudate. In the case of surface impairment, roughness or sharkskinning (Harrison et al., 1985), the extrudate tends to be brittle and short. It has been found earlier that the variables of the Nica extruder affect the quality of the extrudate (Hellén et al., 1992). The effect of granulator variables on the length of the extrudate was investigated in this study.

In most trials the produced extrudate was very short (< 1.5 cm), brittle and rough. Only in those trials where the amount of water was large and also the load of granulator was high, i.e., the speed of powder addition was rapid and the size of the granule outlet was small, was the extrudate longer (1.5–3.0 cm) and smoother. Thus, also during the continuous granulation stage, and not only during the extrusion stage, compaction of the wet mass and the quality of extrudate can be affected. In this study, however, the length of the extrudate seemed to have no effect on the shape, surface, packing or flow properties of the pellets.

Shape and surface structure of pellets

The pellet batches were divided into six shape groups by visual inspection and were denoted by Roman numerals I–VI (Table 3); the higher the class, the rounder the pellets.

The most prominent factors influencing the shape of the pellets were the speed of the friction plate and the residence time. When a higher speed and a longer time were used, the pellets seemed to be rounder. This phenomenon can be seen in the micrographs (Fig. 2A–F) showing typical examples of all six shape groups. The shape varied from long, cylindrical rods through dog-bones and ellipsoids to almost spherical pellets. The pellets in the roundest shape group can be regarded to be spherical enough for coating purposes, although the surface is to some extent rough.

The surface morphology of pellets was dependent on the amount of water used; the greater the amount of water, the smoother the pellets (Fig. 2B, E, F). Anyhow, perfectly smooth surface

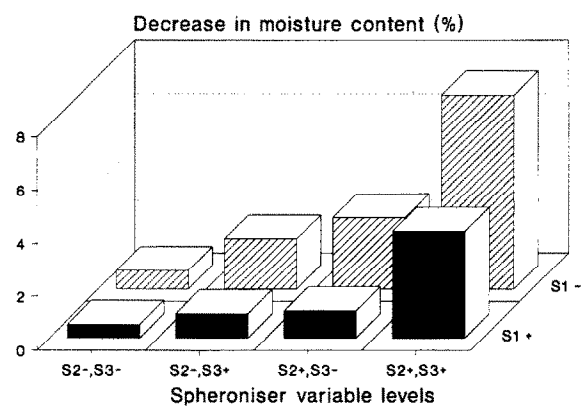

Fig. 1. Decrease of moisture content during spheronisation process. Hatched bars refer to Expts 1–4, and filled bars to Expts 5–8 (Table 3). S1, load; S2, residence times; S3, speed of the friction plate.

was not obtained – on the surface of all pellets small crumbs were found. Similar observations were also made earlier (Hellén et al., 1993a), and it seems to be impossible to explain the presence of these particles by means of any of the process variables. It can be assumed that the plasticity of

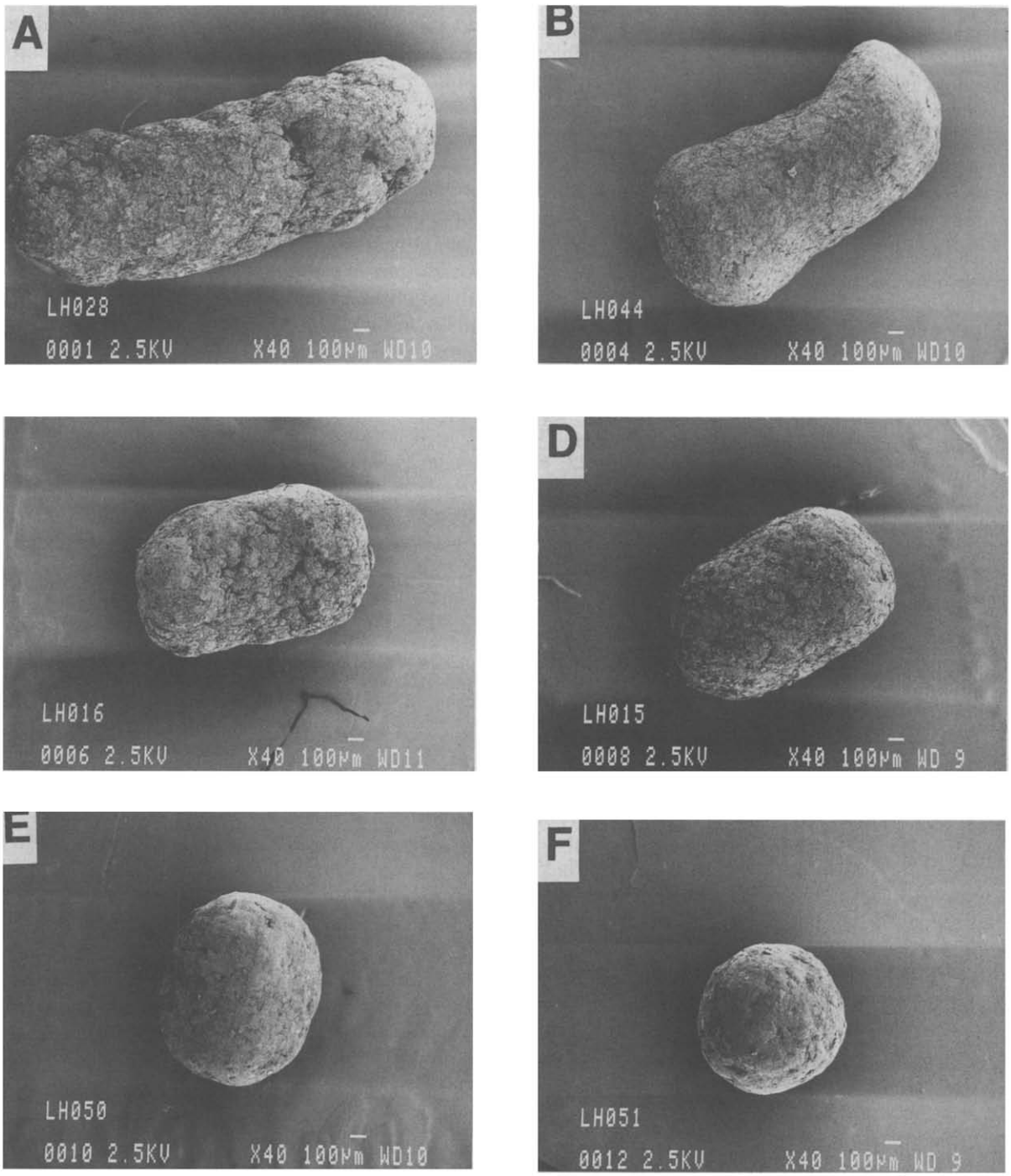

Fig. 2.(A–F) Shape and surface structure of pellets representing shape groups I–VI, respectively.

the wet mass was adequate to produce spherical particles, but insufficient to produce a smooth surface. The surface smoothness was not dependent on the pellet shape.

On the basis of preliminary analysis of variance studies, it was observed that the amount of water had no significant effect on further pellet properties. Therefore, to give an example, the results of pellets produced using lower amounts of water are presented.

Friability of pellets

The friability of pellets varied between 0.3 and 2.7%. The standard deviations between three parallel measurements were quite high, thus no clear statistical differences between batches were observed. Although the numerical values of pellet friability in some cases seemed to be high due to the robust test method used, the roundest pellets (shape groups V and VI), which had friability values $< 1.7\%$, were mechanically acceptable, e.g., for coating purposes on the basis of preliminary studies.

No significant correlation was found between either shape and friability, or surface roughness and friability of pellets.

Packing and flow properties of pellets

Bulk and tapped density The bulk density of pellets varied between 0.46 and 0.69 g/ml and tapped density between 0.52 and 0.77 g/ml. Both densities showed an apparent increase as the processing became more intense through increased loading of the spheroniser ($p < 0.01$), residence time ($p < 0.001$) and speed of the friction plate ($p < 0.001$) – according to correlation analysis, these pellets were also rounder ($p < 0.001$). A similar dependence between spheronising process and bulk density has been reported earlier (Woodruff and Nuessle, 1972; Malinowski and Smith, 1975). The Hausner ratio values varied from 1.07 to 1.15, indicating good flow of pellets.

Flow time The flow time of pellets was mainly affected by the speed of the friction plate ($p < 0.01$). In Table 3 this is seen clearly: every second flow time is shorter, indicating better flowability. The flow time varied from 13.3 to 18.0 s. Significant correlation between shape of pellets and flow time, as well as densities and flow time was found ($p < 0.001$).

In the present study the differences between batches in packing and flow properties of pellets were clearly greater than in an earlier investigation where the variables of the radial screen extruder were evaluated (Hellén et al., 1993a). Obviously, this is due to the greater differences in size and shape of pellets (Allen, 1990). In future, the effect of process variables on size and shape of pellets will be studied closer and more accurately using, e.g., optical microscopy and image analysis.

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