Drug Development and Industrial Pharmacy, 24(5), 401–411 (1998)

RESEARCH PAPER

Investigations on the Influence of the Type of Extruder for Pelletization by Extrusion–Spheronization. I. Extrusion Behavior of Formulations

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ABSTRACT

Three different extruders (the Alexanderwerk gravity feed roll extruder, the Gabler axial, single-screw extruder, and the NICA radial-screw extruder) were compared for their suitability for different placebo formulations and for fenoldopam pellets. A fourth extruder, the experimental ram extruder, was also included in some of the comparisons. Evaluation of the extrusion behavior of the three extruders showed differences as well as similarities among them, depending on the composition of the formulation. Although the NICA and Alexanderwerk units extruded all formulations successfully, the Gabler extruder failed to do so at a content of >60% of soluble ingredients, such as lactose or mannitol. The extrudate surface improved for all extruders with an increase in water content of formulations, but was generally smoother for the Gabler than for the NICA or the Alexanderwerk units. A formulation with colloidal Avicel as spheronization aid showed an identical extrusion behavior for all of the investigated extruders. Of the three extruders, the Gabler unit showed the highest heat generation during extrusion, especially when extruding formulations with a low water content or high contents of soluble excipients. However, when the loss of water during extrusion or spheronization for various formulations was compared, only a two-way ANOVA test on the differences between the water content after extrusion and after spheronization showed a statistically significant difference between the Alexanderwerk or NICA and the Gabler extruder. The two-way ANOVA also proved that this difference is significant only

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for some formulations, e.g., lactose + Avicel PH 101 formulations, but not for Avicel PH 101 formulations.

INTRODUCTION

Hellen (1), Elbers (2), and others reported that the influence of the extrusion parameters on sphere characteristics is very limited and negligible compared to the immense influence of the spheronization step. This is why most authors (3-5) so far have either concentrated solely on the investigation of spheronization parameters or on the description of the extrusion behavior of one distinct extruder type. Baert (6) measured the extrusion forces for some formulations on a gravity feed extruder, a twin-screw extruder, and a ram extruder and Fielden (7) compared the quality of pellets from coarse and fine lactose, produced with either a cylinder or a ram extruder. However, no thorough comparison of the extrusion behavior and the obtained sphere quality related to the different extrusion systems has been conducted.

This paper focuses on a comparison of different extruders, rather than an analysis of the processing parameters of one distinct extruder. Placebo mixes and drug formulations with fenoldopam mesylate as a model for a poorly soluble drug were investigated at different water levels and extruded on an Alexanderwerk gravity feed cylinder extruder (Alexander, Alexanderwerk, Remscheid, Germany); a NICA radial-screw extruder (NICA, Niro-Fielder Ltd., Eastleigh, Hampshire, UK); and a Gabler axial, single-screw extruder (Gabler, Ettlingen). An experimental ram extruder (8) was also included for a limited comparison and the recording of force-displacement profiles. This part of the paper concentrates on the extrusion process itself and the characteristics of extrudates; the sphere quality is described separately (9).

MATERIALS AND METHODS

Extrusion of Placebo and Fenoldopam Formulations

The following materials were used. Avicel® PH 101, CL 611, and RC 591 (Lehmann & Voss, Hamburg, Germany); lactose EP D 80 (Meggle, Wasserburg, Germany); mannitol (Caelo, Hilden, Germany); purified water, DAB 10; fenoldopam mesylate (SmithKline Beecham, Epsom, UK); and succinic acid (Merck, Darmstadt, Germany) (sieved through a 300-μm sieve).

Formulations

The percentage values of mixtures are given as percent of 100% dry solids, and the water contents are calculated as percent of wet granulate.

Avicel PH 101 + 48-57% water mixtures were used as a model mix with ideal properties for spheronization and a high water binding capacity.

Lactose was used as a model for a highly water-soluble component in concentrations of 50-80%. Formulations of lactose + Avicel PH 101 were as follows: 50 + 50, 35-40% water; 60 + 40, 36-38% water; 66 + 34, 31-36% water; 75 + 25, 25-29% water; and 80 + 20, 25-34% water.

Mannitol + Avicel PH 101, 70 + 30, 27-33% water, which has been used as a model by Hellen (10) for the evaluation of the NICA system, is generally less suitable for extrusion-spheronization than the more soluble lactose used by most of the other investigators. It therefore represents a model for rather difficult formulations.

Succinic acid + Avicel PH 101, 80 + 20, 25-30% water was investigated as a model for a component with a relatively low water solubility and also because of its use as a pH-adjuster for fenoldopam pellets.

Fenoldopam mesylate + succinic acid + Avicel PH 101 (40 + 40 + 20), 31-34% water was used as a model formulation for the weakly basic drug in combination with its pH-adjuster (9).

Avicel CL 611 + Avicel RC 591 + lactose (20 + 10 + 70), 28% water was used as a formulation containing colloidal grades of Avicel as a spheronization aid instead of Avicel PH 101.

Processing

All dry ingredients were mixed in a Kenwood Chef mixer with a K-shaped mixing tool, metal bowl, and Plexiglas lid (Kenwood Ltd., Hampshire, UK) for 15 min at a setting of 1-2; Water was added as granulation liquid in three equal portions over 10 min at a maximal setting of three digits. The wet granulate was extruded immediately after granulation. Optional spheronization was done on 200 g loads and at a speed of 1000 rpm for 15 min on a 23-cm. spheronizer with cross-hatch disk (Caleva, Dorset, UK). If not needed for water content determination or further processing, the extrudate was dried in a thin layer in an oven (Memmert, Schwabach) at 40°C for 24 hr.

Alexanderwerk GA 65 extruder includes a 1.0 mm diameter × 0.8 mm thick die cylinder with drilled holes. The granulate is manually fed onto the counter-rotating rolls at a standard extruder speed of 8 digits at 132 rpm. This gravity feed roll extruder was modified by protecting the material feed section by an additional PTFE seal from the greased section of the rotating cylinders.

Two cylinders, one solid and one perforated, rotate in opposite directions and the wet granulate is gravity fed onto them. The wet granulate adheres to the knurled surface of the solid cylinder, forms a thin layer on its surface, and is then pressed through the die of the second cylinder. The exerted pressure depends on the length and the diameter of the holes. The granulate is thus compacted into extrudate, which is cut into segments of 0.5–1 cm by a scraper blade, within the interior of the performed cylinder. Even small amounts of about 100–200 g of wet material can be processed, because only the material adhering to the pressure cylinder is lost during the process.

Gabler E40/10D axial single-screw extruder includes a 1.0 mm diameter × 1.0 mm thick punched die. The entire granulation batch is filled in the hopper and the extrusion head then works at a constant speed of 60 rpm. In order to compare all extruders under the same conditions, the barrel and extrusion head were not cooled during extrusion, despite the presence of a cooling jacket.

The horizontally rotating feeder transports the wet mass to the barrel below, where the rotating screw with its regularly spaced flights transports the mass from the feed zone along the axis of the barrel to the compression zone and through the axial screen at the end of the barrel. After passing the screen, the extrudate falls off by its own weight, resulting in strings of up to 30 cm. During the transport through the barrel, air is forced out from between the agglomerates and from the interstitial voids, thereby compacting the mass prior to extrusion. The pressure created during this movement depends on the screw geometry and the rheology of the paste, but is generally higher for single-screw extruders than for twin-screw extruders. Minimum batch sizes are about 400–500 g of wet granulate, because a relatively large amount of stagnant material is built up between the screw and the die.

NICA E 140 radial screen (basket) extruder includes 1.0 mm diameter × 1.0 mm thick punched die. The entire batch is filled into the hopper. The feeder rate of 60 rpm and extrusion speed of 50 rpm can be adjusted separately.

The granulate is fed from the hopper to a central feed blade, which counter-rotates to the rotating disk below. On the disk, the wet material is then forced through the encircling extrusion screen by angled impeller blades. From the exterior of the screen, the extrudate falls off by its own weight and is broken into strings of about 2–10 cm, depending on the cohesiveness of the mass. High pressure and friction forces are exerted on only a small amount of material and only during extrusion, which eliminates both excessive heat generation and the creation of a moisture gradient between the wet mass and the extrudate. The dead volume is about 15 g per baffle.

The temperature during extrusion was measured directly at the extrusion screen and in the extrudate leaving the die with a portable, digital thermometer.

An experimental ram extruder after Overstone and Benbow (8) with Lloyds MX55 load cell, is equipped with an X-Y recorder to record force–displacement profiles, single-hole die 1 mm diameter × 4 mm thick (Lloyds Instruments, Southampton, UK). The barrel with the die fitted at its bottom is filled with approximately 50 g of granulate, which is packed tightly by stamping with a plastic stick. The filled barrel is placed on the load cell, which is lowered manually until contact with the barrel. Then the cell is further lowered automatically at a constant speed of 200 mm/min for 0.8 min. The extrudate is collected in plastic bags.

The load cell reports the power consumption and a displacement transducer reports the ram displacement to a PC. The exerted pressure depends on the rheological properties of the wet mass, the ram speed, and the length/diameter ratio (L/D) of the hole. The ram extruder exerts high pressure on the material, generating more heat and a higher water movement than most of the other extruders, especially for formulations with poor rheological properties.

Determination of the Moisture Content as Loss on Drying

Moisture contents of powders, granulates, extrudates, and wet pellets were determined by filling about 20 g of sample in weighed Petri dishes and drying them in a vacuum oven RVT 360 (Heraeus, Hanau, Germany) at 60 ' and 100 torr for 24 hr. Then the filled dishes were weighed again and the loss on drying was calculated as percent of the sample weight.

Photomicrographs

An SMZ2T stereomicroscope (Nikon, Duesseldorf, Germany) with intralux 5000-1 lamp (Volpi, Switzerland) and a camera with adapter for microscope (Nikon) were used. Photos were taken using a magnification of 10× and 2×.

Statistics

All statistical calculations were done with the use of Ref. 11 and the software program Quattro Pro for Windows 5.0, Borland International, Inc.

RESULTS AND DISCUSSION

Ease of Extrusion and Quality of the Extrudate

Table 1 gives an overview of the behavior of the different formulations in the four extrusion systems. It shows that the NICA and the Alexanderwerk extruders are suitable for all formulations, while only those lactose formulations containing at least 40% Avicel PH 101 were extruded successfully by the Gabler extruder. The mannitol formulations could not be extruded with the screw extruder, and the ram behaved similarly to the single-screw extruder in being unsuitable for all of the formulations. The four extruders also exhibited evident differences in heat generation during extrusion and the surface structure of extrudates.

The Alexanderwerk rotary cylinder extruder generates shear stress only on those parts of the wet mass which are either held in the nip between the two cylinders or flow through the die land. Therefore no excessive heat generation from friction and compression over long distances takes place throughout the process. The L/D ratio is decisive for the pressure drop P_2 in the die land and the extrusion force that forms the wet mass into a distinctly formed extrudate, but also influences the surface quality of extrudates (12).

$$P_2 = 4 \cdot \tau \cdot (L/D) \qquad (1)$$

where τ = wall shear stress in (Pa), L = die length, and D = hole diameter.

Poor-quality extrudates might exhibit a rough surface texture, which is described as shark-skinned, because severe fissures protrude the surface. Such defects are caused by small die lengths, large die diameters, and high extrusion pressures and are also influenced by the die geometry and the composition of formulations (12). Because the investigated L/D ratio of 0.8 for the Alexanderwerk was rather small, the observed poor quality of extrudate even for an optimally wetted formulation [Figure 1(a)] has to be attributed to this low die length. For the rotary cylinder extruder, the process of extrusion ensures a complete filling of the die and therefore results in a cylindrical extrudate that might be short and shark-skinned but is never fragmented. Fragmentation is observed when formulations are extruded from dies that are filled only partially. When increasing amounts of water and soluble compounds were added, (both of which aid in the binding force of the material), the surface defects were less severe, but did not completely disappear. This was endorsed by the observations made when formulations of colloidal Avicel graders were extruded. Other than Avicel PH, these grades contain sodium carboxymethylcellulose as a binder and lubricant, which reduces the wall shear stress in the die and increases the strength of the extrudate. Extrudates are therefore much smoother and almost identical, regardless of the type of extruder used. They are, however, also longer, because these Avicel grades express more elastic, rather than plastic properties. Being more flexible, the extrudate is less prone to breakage under its own weight. This lack of rigidity might present a problem for further processing.

The NICA radial screw extruder behaves in a similar fashion to the Alexanderwerk unit and exhibits the same tendency for surface defects at small L/D ratios. This was also demonstrated by Vervaet (13), who showed a substantial improvement in the extrudate's quality when screen thickness was increased from 1 to 2 mm for a 1-mm diameter die. The punched die used in the described trials shows rather sharp edges at the entry and exit of the die, caused by the punching process. This further adds to the tendency for the surface of the paste to tear when it enters or leaves the die land (14). The fragmentation observed, especially at lower water contents and in more fragile pastes, demonstrates this drawback of the punched screens. Other screens, such as those with cylindrical drilled or tapered profiles, are successful in preventing these surface defects and the fragmentation of extrudates. They are reported to produce good quality extrudates and subsequent pellets from formulations that resulted in either milling or agglomeration when formulations were extruded with a punched screen (15). For higher water contents, extrudates show less severe shark-skinning than comparable Alexanderwerk extrudates, as visible in Figure 1(b), but are otherwise quite similar; heat generation does not present a problem.

Table 1

Comparison of the Extrusion Behavior and the Quality of Extrudates

Extruder	Extrusion Successful	Extrudate Quality	Temperature During Extrusion
		Avicel PH 101 + Water	
A	Yes	At 48% water, extremely shark-skinned, but not fragmented; at higher water contents (55%) still rough	No warming of material
G	Yes	At 50% water, smooth extrudate without any shark-skinning; length and surface quality increase with increasing water contents	50% H_2O: 42–57°C; 57% H_2O: 32–37°C
N	Yes	3-cm-Long extrudate that shows less severe shark-skinning than the Alexanderwerk extrudate; at 48% water no real cylinders appear, but mostly fragments are observed; at higher water contents (52%) real cylinders are formed, with reduced surface defects	–[a]
R	Yes	Severe shark-skinning of extrudate at high ram speeds (200 mm/min) for all water contents; smooth extrudate at lower ram speeds (50–100 mm/min)	Quite hot, especially at low water contents
		Lactose + Avicel PH 101 (50 + 50/60 + 40) + Water	
A	Yes	Similar to pure Avicel PH 101 formulations	–[a]
G	Yes	Extrudate is smooth, without any severe surface roughness; extrudate length increases to 10–15 cm as water contents increase; generally more rigid extrudate than pure Avicel PH 101 formulations	Generally > 50°C, but lower for high H_2O contents
N	Yes	Similar to pure Avicel PH 101 formulations	–[a]
		Lactose + Avicel PH 101 (80 + 20/75 + 25/66 + 34) + Water	
A	Yes	Short, shark-skinned extrudate, or at least extremely rough surface (high water contents); no fragmentation observed other than for extremely dry formulations	–[a]
G	No[b]	The few extrudate strings are very rigid and in many cases grey instead of white; low and high water contents show the same poor extrusion behavior; extreme water movement between the extrudate and the plug and within the extrudate (start to end); surface of extrudate varies from smooth to rough, but shows very limited shark-skinning	Extremely hot, (visible water evaporation)
N	Yes	Shark-skinned, at higher water contents rough surface structure; as the lactose content increases, the fragmentation of extrudate increases for dry formulations, but wet mixtures result in a cylindrical extrudate	–[a]

(continued)

Table 1. *Continued*

Extruder	Extrusion Successful	Extrudate Quality	Temperature During Extrusion
		Mannitol + Avicel PH 101 (70 + 30) + Water	
A	Yes	Similar behavior as lactose formulations, but even shorter cylinders	–[a]
G	No[c]	Grey extrudate with surface defects and extreme water movement; breaks into rather short cylinders of about 2–3 cm	Extremely hot
N	Yes	Similar behavior as lactose formulations, but less fragmentation and better surface quality at higher water contents	–[a]
		Fenoldopam + Succinic Acid + Avicel PH 101 (40 + 40 + 20) + Water	
A	Yes	Still quite rough, short extrudate; rather dense structure	–[a]
G	Yes	Smooth, white extrudate; brittle and thus shorter at lower water contents (31%), while soft and longer at higher water contents	Hot (31% H_2O), warm (34% H_2O)
N	Yes	Almost smooth, 5- to 6-cm-long extrudate; no fragments, but strong cylinders; gets sticky at higher water contents (34%)	32% H_2O: 27–28°C; 34% H_2O: 20°C
R	Yes	Shark-skinned, but otherwise quite good, long extrudate; reduced surface defects at lower ram speeds	Hot
		Succinic Acid + Avicel PH 101 (80 + 20) + Water	
A	Yes	Soft, fragile extrudate; short cylinders and fragments at 25% water	–[a]
G	No		
N	Yes	About 2-cm-long, cylindrical extrudate with reduced shark-skinning and a reduced amount of fragments	–[a]
R	No		
		Avicel CL 611 + Avicel RC 591 + Lactose (20 + 10 + 70) + 28% Water	
A	Yes	Smooth, 5-cm-long extrudate, despite the action of the scraper blade; extrudate tends to stick to the interior of the die cylinder and to other strings of extrudates	–[a]
G	Yes	Smooth, 10- to 20-cm-long extrudate of well-formed cylinders; easily extruded, but too flexible to be broken into shorter strings	Almost no warming
N	Yes	Smooth, almost 20-cm-long extrudate without any shark-skinning; flexible, but still rigid enough to be broken into shorter strings	–[a]
R	Yes	Soft, very long (30 cm) extrudate that curls up under its own weight without breaking; no stickiness	–[a]

Cylinder extruder (Alexanderwerk = A), axial-screw extruder (Gabler = G), radial-screw extruder (NICA = N), and ram extruder (ram = R).

[a] Temperature not evaluated.

[b] Extrusion takes place through only 1–3 central holes; extreme water movement between extrudate and plug.

[c] Only the 33% water formulation could be extruded in a similar manner as the lactose + Avicel PH 101 (80 + 20) mixtures.

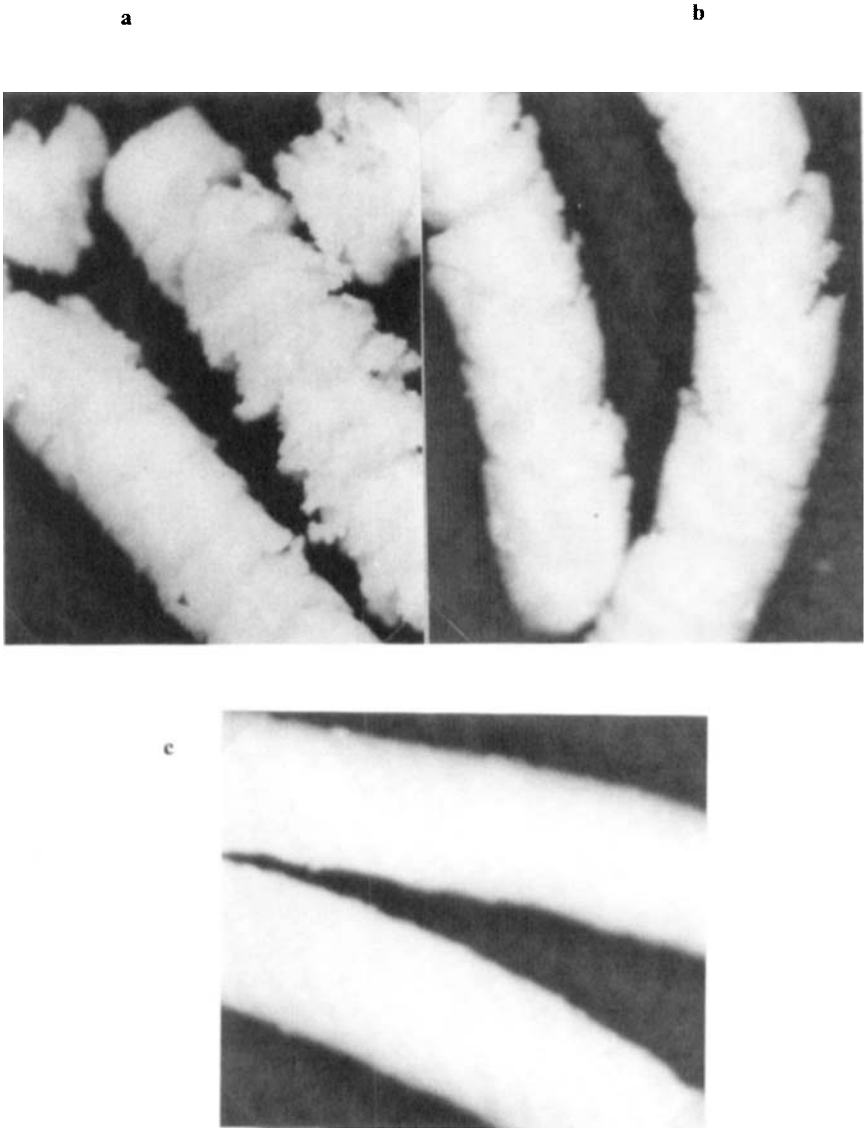

Figure 1. Extrudates produced from a formulation of 60% lactose + 40% Avicel PH 101 at a water content of 33% with the (a) Alexanderwerk rotary cylinder extruder; (b) NICA radial-screw extruder; and (c) Gabler single-screw extruder.

The Gabler, a single-screw axial extruder, showed a generally much smoother surface structure of extrudates [Figure 1(c)], than the other two extruder types, despite the same low *L*/*D* ratio of 1.0 and the punched die. This was attributed to the different extrusion process, which causes an increase in pressure as the wet mass is transported along the barrel. A pressure gradient is thus generated related to the barrel diameter and length, the screw geometry, and the composition of the formulation, until the mass eventually flows through the die. This consolidation prior to the actual extrusion and the more gradual increase in force seem to increase the strength of extrudates and reduce their tendency to exhibit surface defects. Conversely, this also leads to an increase in heat generation and thus a higher thermal exposure of materials, which facilitates the movement of water between the wet mass and extrudate and might also be detrimental to heat-sensitive compounds. As the resistance to flow increases for pastes with decreasing amounts of the readily deformable Avicel PH 101, the flow in the barrel and through the die becomes more difficult. The pressure and shear exerted onto the mass increase. These formulations showed low throughput rates, high processing temperatures, and an extreme movement of water within the formulation, resulting in a higher water content for the extrudate than for the plug in the barrel. This was observed for formulations of lactose and mannitol with less than 40% of Avicel PH 101, which therefore could not be extruded successfully with the single-screw extruder. Other authors, such as Kleinebudde and Lindner (16), who worked with a twin screw extruder, could extrude mixtures with as much as 90% lactose and 10% Avicel PH 101 successfully, because in a twin-screw extruder the flow through the barrel is provided by the transport of the two corotating screws.

Despite the different results for Avicel PH 101 + lactose (25 + 75) + water formulations, all extruders were equally successful in extruding a formulation containing 30% of Avicel CL/RC instead of Avicel PH 101. Quite similar extrudates of considerable length and a smooth surface were obtained for all extruders. The investigated fenoldopam formulation (a weakly basic drug of poor water solubility) also showed a similar extrusion behavior for all extruders; formulations containing only succinic acid could not be processed on either the ram or the axial, single-screw extruder, indicating a poor rheology for this formulation.

The ram extruder caused a rather high heat generation, comparable to that observed for the single-screw extruder, which was expressed most visibly for formulations with low water content or high amounts of lactose. In contrast to the other investigated extruders, the ram showed a severe influence of extrusion speed on the surface quality of extrudates. As ram speed decreased, shark-skinning was reduced and the extrudates got smoother. A reduction in ram speed, however, also resulted in an increased water movement between the extrudate and the plug.

The single-screw extruder and the ram extruder, which both exert rather high pressures, were capable of producing good extrudate from formulations with at least 40% of the readily deformable Avicel PH 101 or 30% of colloidal Avicel grades. The screw extruder was, however, much more robust as to the water content required for the formulations, while the ram extruder was highly sensitive to both water content and ram speed.

Formulations with more than 60% of highly water soluble components or poor rheology could only be processed successfully when extruded with either the rotary cylinder extruder or the radial basket extruder. These extruders were generally quite similar in their extrusion behavior, but differed in the surface quality of extrudates for identical formulations. The rotary cylinder extruder showed a slightly higher sensitivity to the water content of formulations than did the radial basket extruder.

Loss of Water During Extrusion–Spheronization

The increased sensitivity of the axial screw extruder to water movement, compared to the other two extruders, was believed to manifest itself in a higher loss of water during extrusion. Therefore, the loss of water during extrusion and spheronization was evaluated in order to investigate whether there is any dependence on either the type of extruder or the formulation. The water content of granulates was taken as 100% to calculate the percent loss of pelletization steps, or the difference between the content after extrusion and after spheronization in percent. When we compared the average loss of water for each of the three investigated extruders in Table 2, the water content after extrusion showed *no significant differences* ($p < 0.05$) *for any of the* extruders or for the different formulations. The greater water loss observed with the screw extruder was not statistically significant, indicating that water was not actually lost during the extrusion process, despite the increased water movement. Water contents of extrudates were similar to the original content of the granulates, showing a decrease of only 2–4%. Water, however, is not distributed homogeneously within the extrudate for all extruders. The NICA and Alexanderwerk do not exert excessive pressure during extrusion and the water is therefore still homogeneously distributed throughout the extrudate. During spheronization, water is centrifuged to the surface of the pellets, from which it dries

Table 2

Comparison of the Loss of Water During Extrusion and Spheronization for Different Extruders

	Alexanderwerk	Gabler	NICA
Loss of water in percent after extrusion: mean of $n = 25$, ± SD	2% ± 1.3	3% ± 4.8	2% ± 1.5
Loss of water in percent after spheronization: mean of $n = 25$, ± SD	9% ± 3.0	12% ± 7.0	9% ± 3.4

off, leading to a lower total water content for the spheronized product. For severe water movement (observed for the Gabler extruder) the water is not equally distributed, but already shows a water gradient for the extrudate. Therefore, water can be removed much easier during spheronization, causing a significantly larger difference between the water content after extrusion and after spheronization. The actual differences, however, always depend on the formulation, being greater as the content of readily soluble components increases and Avicel PH 101 concentrations decrease. Formulations with mostly poorly soluble ingredients showed generally less marked differences, and when the spheronization step alone is considered for all formulations together, the differences in the water contents were still not significant on the 95% level.

Therefore, a two-way ANOVA was tabulated for the loss of water after extrusion, spheronization, and the difference between extrusion and spheronization for each extruder, thus taking the influence of the formulations into account. Table 3 shows that there is still no significant difference for the extrusion step ($p < 0.05$). For the spheronization step, however, the difference between the Gabler extruder and the NICA extruder is significant; the NICA unit shows still higher water contents after spheronization than the Gabler. When the differences after extrusion and after spheronization are analyzed together, rather than each step separately, this becomes even more apparent; the difference is not only significant for the NICA and Gabler units, but also for the Alexanderwerk and Gabler interaction.

That this different behavior of the three extruders strongly depends on the formulations can be seen not only from the ANOVA table, but also from the comparison in Fig. 2. For Avicel PH 101 formulations and fenoldopam + succinic acid (1+1) formulations, the loss of water was only slightly higher when extruded on the axial-screw extruder, and showed about the same variability as for the other two extruders. The lactose formulations, however, not only showed a higher mean value for the Gabler extruder, but also a much higher variability in their loss of water.

Table 3

Table for Two-Way ANOVA Without Replicates to Test the 95% Significance of the Loss of H_2O During Extrusion and Spheronization, and the Difference Between Extrusion and Spheronization for the Alexanderwerk (A), the Gabler (G), and the NICA (N) Extruder

	SS	df	MS	*F*	*F* (Critical) for 95% Significance	LSD test *t* (Critical) for 95% Significance for 22 df = 2.08
Extrusion						
Within extruders	33.53	11	3.048	2.185	2.258	
Between extruders	1.64	2	0.820	0.588	3.443	
Residual	30.69	22	1.395			
Total	65.86	35				
Spheronization						
Within extruders	327.96	11	29.81	3.047[a]	2.269	G/N = 2.839[a] A/G = 1.951 A/N = 0.888
Between extruders	82.53	2	41.27	4.217[a]	3.443	
Residual	215.27	22	9.79			
Total		35				
% Extrusion - % Spheronization						
Within extruders	213.76	11	19.89	2.543[a]	2.269	A/G = 2.263[a] A/N = 0.562 G/N = 2.825[a]
Between extruders	69.94	2	34.97	4.471[a]	3.443	
Residual	172.07	22	7.82			
Total	463.769	35				

[a] Significant values.

df = Degrees of freedom, SS = sum of squares, MS = mean of squares, LSD = least significance difference, *F* = *F* value as a result of the ANOVA analysis, *F* (critical) = minimum *F* value at which the difference is significant, *t* (critical) = minimum *t* value at which the difference between the extruders is significant, when subjected to the LSD test.

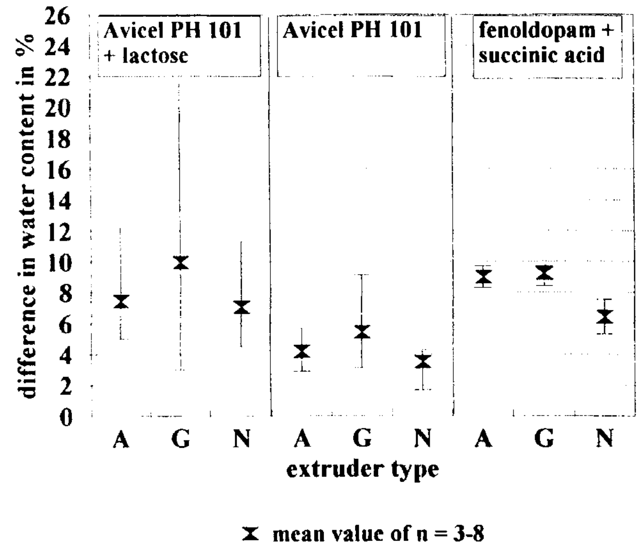

Figure 2. Comparison of the difference in water content after extrusion-spheronization for the Alexanderwerk (A), the Gabler (G), and the NICA (N) extruders for formulations of Avicel PH 101 + water, lactose + Avicel PH 101 + water, and fenoldopam mesylate + succinic acid + Avicel PH 101 + water.

Force–Displacement Profiles for the Ram Extruder

To determine the forces required for the extrusion of each of the formulations, force–displacement plots were obtained from the experimental ram extruder. They characterize the distinct rheological properties of each formulation and are useful in showing general differences between them. However, the exact values are only valid for the ram extruder and the experimental settings under which they were obtained.

All plots show the same profile, with an initial compression stage, a steady state flow period of variable length, and a final forced flow pattern as described by Harrison (17). The length and extent of the individual stages, however, depend on the formulation and are different for the five plots in Fig. 3. All formulations, other than the Avicel CL/RC formulation, showed quite short compression stages, before a sudden increase in the force started the flow of material through the die. The force required for this onset of flow depends on the formulation and the water content of the formulation. Higher water contents result in lower extrusion forces for Avicel PH 101 + water formulations because more and more voids are filled by water, generating a lubricating layer and improving the plasticity of the wet mass. Higher amounts of lactose present in the formulation lead to an increase in force as the material exhibits a larger resistance to flow and gets quite hot under the exerted pressure. The Avicel PH 101 + water formulations show a steady state extrusion over most of the time axis, while the Avicel PH 101 + lactose mixtures show only a very short, if any, steady state flow and thereafter, a forced flow pattern. Avicel CL/RC mixtures require generally lower extrusion forces and exhibit a purely steady state flow pattern even for mixtures containing 70% lactose. The compression stage prior to extrusion is, however, longer for these mixtures than for the Avicel PH 101 mixes. The colloidal Avicel grades not only reduce the wall shear stress of a formulation, but also its plastic properties, while increasing its elastic properties. Therefore, a larger displacement is required to induce flow through the die. Harrison (18)

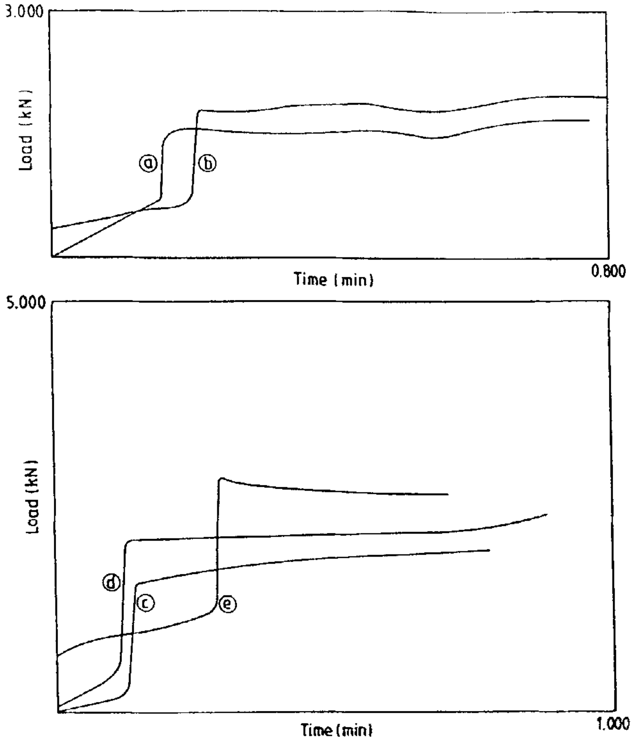

Figure 3. Force–displacement plots for ram extrusion with a 1.0 × 4.0 mm, single-hole die on an instrumented Lloyds press at a constant ram speed of 200.0 mm/min. (a) Avicel PH 101 + water, 50%, F_{max} = 1.69 kN; (b) Avicel PH 101 + water, 52%, F_{max} = 1.65 kN; (c) Avicel PH 101 + lactose (50 + 50) + water, 39%, F_{max} = 2.04 kN; (d) Avicel PH 101 + lactose (20 + 80) + water, 27%, F_{max} = 2.40 kN; and (e) Avicel RC/CL + lactose (10 + 20 + 70) + water, 28%, F_{max} = 2.19 kN.

regarded such a behavior as a drawback to the extrusion behavior of a formulation, because it reduces the throughput rate.

CONCLUSIONS

Because the different types of extruders exhibited a strong influence on the extrudate quality of some formulations, and showed almost no impact on other formulations, the correlation between these extrusion properties and the sphere quality of pellets produced from these extrudates must be evaluated as an additional step. Only then would it be possible to decide which extruder exhibited relevant advantages or disadvantages over another for individual formulations. Furthermore, this would also be helpful when formulations are to be transferred from one extruder to another. These points will be discussed in detail in a separate paper.

ACKNOWLEDGMENTS

We wish to express our thanks to the Fond der Chemischen Industrie for grants to support research work and to the company Gabler Inc., Ettlingen, Germany, for the opportunity to work with the axial, single-screw extruder. Special thanks are also due to Prof. J. M. Newton, Department of Pharmaceutical Technology, University of London, for the opportunity to work with the instrumented ram extruder in his laboratory.

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