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RESEARCH PAPER

Investigations on the Influence of the Type of Extruder for Pelletization by Extrusion–Spheronization. II. Sphere Characteristics

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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. The successful spheronization of extrudates from each of these extruders requires the correct water content. This water content, however, is different for each of the formulations and for each extruder. Generally, the Gabler unit required the highest amounts of water for a successful spheronization, yielding ≥90% between 710 and 1250 μm. The NICA unit needed much less water for the same formulation, and the Alexanderwerk unit required even less water than the NICA unit. Pellet sphericity was also strongly dependent on the correct water content of formulations, but was generally better for pellets produced with the Alexanderwerk or NICA units. A two-way ANOVA test for the individual formulations showed a significant difference in the mean particle size of batches produced with the NICA or the Alexanderwerk and the Gabler extruder. No significant differences could be found between any of the Alexanderwerk or NICA batches. Both extruders showed a linear dependence of the mean particle size on the water content of formulations, but the Gabler extruder showed an almost unchanged particle size over a wide range of water contents, provided that the formulation could be extruded successfully.

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Batches that were extruded on the NICA unit showed a significantly lower bulk density than comparable Alexanderwerk or Gabler batches. Comparing the true density of pellets, we found that significant differences could only be stated for Avicel PH 101 + water batches and only for the NICA/Gabler interaction. True density increased for all three extruders with increasing amounts of soluble components and with increasing water content. The NICA batches also exhibited a significant difference of the Hausner factor from the other two extruders, but no differences could be found in the friability of pellets.

INTRODUCTION

This paper continues the evaluation of three different extruders that was carried out to compare feasibility for the production of pellets from selected formulations, and advantages and disadvantages of each extruder (1). Placebo mixes and drug formulations 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, Ettingen, Germany). Part I focused on the extrusion behavior; part II concentrates on the sphere characteristics of the pellets after spheronization. Although the extrudate and its features are not the main interest for the formulator, the quality of these extrudates influences the characteristics of the resulting pellets (such as sphere size, sphericity, friability, or density). These characteristics were determined in the following study. Especially because the different extruder types were shown to produce completely different extrudate quality for some of the formulations, but quality was quite similar for others, the impact of extrudate quality on sphere quality was considered to be worthy of further study.

MATERIALS AND METHODS

Extrusion of Placebo and Fenoldopam Formulations

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) were used.

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. For more details, please refer to Ref. 1.

Avicel PH 101 + 48–57% water was used as a model mixture 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%. Mannitol + Avicel PH 101, 70 + 30, 27–33% water; succinic acid + Avicel PH 101, 80 + 20, 25–30% water; fenoldopam mesylate + succinic acid + Avicel PH 101 (40 + 40 + 20), 31–34% water; and Avicel CL 611 + Avicel RC 591 + lactose (20 + 10 + 70), 28% water, were also used.

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. Spheronization was done in 200-g loads and a speed of 1000 rpm for 15 min on a 23-cm. spheronizer with cross-hatch disk (Caleva, Dorset, UK). Pellets containing Avicel CL/RC were spheronized at 1240 rpm. The pellets were dried in a thin layer in an oven (Memmert, Schwabach) at 40°C for 24 hr.

The following extruders were used: Alexanderwerk GA 65 extruder with 1.0 mm diameter × 0.8 mm thick die cylinder with drilled holes; Gabler E40/10D axial, single-screw extruder with 1.0 mm diameter × 1.0 mm thick punched die; NICA E140 radial-screen (basket) extruder with 1.0 mm diameter × 1.0 mm thick punched die (Niro-Fielder Ltd., Eastleigh, Hampshire, UK); and experimental ram extruder after Overstone and Benbow (2) with Lloyds MX55 load cell, equipped

with an X-Y recorder to record force–displacement profiles, single-hole die 1 mm diameter × 4 mm thick (Lloyds Instruments, Southampton, UK).

Determination of the Particle Size and Size Distribution of Pellets

A Retac 3D vibrating sieve shaker (Retsch, Haan, Germany) was used to determine particle size. Analytical standard sieves had a mesh size of 710, 800, 900, 1000, 1120, 1250, 1400, and 2000 μm; 100–150 g of pellets was sieved for 20 min at a setting of 40 digits.

Sieve fractions were characterized as percent weight of each oversize sieve fraction in a histogram and as summation of the percent undersize sieves. The percentage between 710 and 1250 μm was considered as the yield of pellets showing the desired size and was used for the characterization of successful pelletization with a rather narrow size distribution of less than 540 μm.

Mean particle size of weight fractions was calculated as the arithmetic mean of sieve sizes:

$$\bar{d} = \frac{\Sigma x_i \cdot d_i}{100} \quad (1)$$

where x_i = the mean of the upper and lower limits of the sieve fraction, and d_i = the percentage of the sieve fraction i.

Determination of the True Density

An automated gas pycnometer (Autopycnometer 4.100, Grimm, Ainring, Germany) with helium as a test gas was used. The true volume V_S was determined according to the equation

$$V_S = V_{SC} - \frac{P_i - P_0}{P_f - P_0} \cdot V_r \quad (2)$$

where V_{SC} = volume of the empty cell, V_r = volume of the reference cell, P_i = pressure of reference cell when filled with helium, P_f = pressure of sample cell when filled with helium, and P_0 = pressure of evacuated system. The true density was calculated by the sample size and the true volume was calculated in g/cm^3.

Determination of Bulk Density and Hausner Factor

Pellets (100 g) of the size 710–1250 μm were placed in a 100.0-ml volumetric cylinder and their volume was determined. The bulk density was calculated as g/ml in triplicate for each batch. The coefficient of variation (CV) was 0.1–1.5%.

The cylinder was then tapped 1250 times in a stamp volumeter (Engelmann AG, Ludwigshafen a. Rhein, Germany) and the volume determined again afterward to calculate the tapped density. The CV was 0.1–0.9%.

The Hausner factor was calculated as the ratio between the tapped density and the bulk density.

Friability

A friabilator similar to the Roche® friabilator, but built out of stainless steel to prevent electrostatic charging of the pellets on rotation, was used.

About 10 g of pellets of the size 710–1250 μm was rotated in the friabilator together with 200 glass beads (2 mm diameter) at a constant speed for 10 min. The pellets were then sieved through a 710-μm sieve again and the weight loss of the sample was calculated as percent friability. All batches were determined in duplicate.

Statistics

All statistical calculations were done with the use of Ref. 3 and the software program Quattro Pro for Windows 5.0, Borland International, Inc.

RESULTS AND DISCUSSION

The following describes the ability of the different extrudates to transform into spherical pellets of about 1 mm mean particle size at a narrow size distribution, i.e., ≥90% between 710 and 1250 μm, when spheronization parameters were kept constant for all formulations.

The Spheronization of Extrudates into Pellets

The spheronization of extrudates revealed even more distinct differences between the different types of extruders than had already been observed during extrusion (1). The sphericity of pellets depended strongly on the properties of the extrudate, as did the size distribution and the mean pellet size. The addition of too much water led to agglomeration and larger pellets, and lower water contents caused a wide size distribution with excessive attrition and large amounts of fines. Pellet sphericity was generally better for larger pellets than for batches with an increased amount of fines. This sensi-

tivity to attrition was more pronounced for the formulations with none or only small amounts of soluble excipients. Extrudates that consisted in a major part of fragments rather than cylinders tended to be more prone to both attrition at low and agglomeration at high water contents.

For increasing amounts of Avicel PH 101, the water content, at which homogeneously sized pellets of about 1 mm were obtained, increased. However, this increase in water content and the sensitivity of spheronization to changes in the water content were different for each of the three investigated extruders. Although the Alexanderwerk and NICA extruders required a water content of 50 and 52%, respectively, for Avicel PH 101 + water mixtures, the Gabler unit successfully transformed any water content between 50 and 57% in spheres with a narrow size distribution. Therefore, not only the water content, but also the sensitivity of extruders to changes in the water content, was different for each extruder. The Alexanderwerk unit allowed only 1:1 (Avicel PH 101:water) mixtures to be processed into spheres, the NICA unit was best at a ratio of 1:1.1, and the Gabler unit was best at a ratio of 1:1.2. Slightly lower or higher water contents led to either increased attrition or agglomeration for the first two units, but the Gabler tolerated a range of 1:1–1:1.3 without any change in the yield. The water in the formulations produced by the latter extruder was incorporated into the formulations at a higher pressure, leading to a higher densification of the extrudate. Thus water was also retained more effectively by the Avicel during the subsequent spheronization. Water was centrifuged to the pellet surface during spheronization (4), but only about 10% of the water dried off from there during spheronization, with little difference in the loss of water observed for the three different extruders. Higher water contents of extrudates might thus result in overwetted surfaces, when the water is not retained strongly enough inside the spheres. Such overwetted surfaces then tend to agglomerate, as observed for the wet formulations in the Alexanderwerk and NICA extruder.

Large differences in the water movement and the loss of water were, however, observed among the Gabler extruder and the other two extruders, for formulations with large amounts (>60%) of the soluble sugars lactose or mannitol. For increasing amounts of soluble components, successful spheronization, even with the Gabler extruder, depended more and more on the correct water content of formulations, because the amount of Avicel PH decreased in favor of the lactose content. The total water content required for a high yield between 710 and 1250 μm was, however, still about 2% higher for the Gabler unit than for the NICA unit and about 5% higher than for the Alexanderwerk unit. At a low water content the highly compacted mixtures of lactose and Avicel PH resulted in less spherical dumbbells, but good spheres were obtained for higher water contents. The dry formulations thus seemed to exhibit too much stiffness and too little plasticity for the reduced amounts of Avicel PH to be rounded properly. Higher water contents induced a higher plasticity and formulations were therefore successfully rounded. As the formulations grew more prone to water movement during extrusion, i.e., with increasing amounts of lactose or mannitol, the cylinder extruder and radial-screw extruder were superior to the axial, single-screw extruder, resulting in small, spherical pellets. As a result of the lower pressure applied to the formulations and the shorter exposure to the pressure, the danger of water movement was reduced and the controlled pelletization thus improved. The NICA extruder, however, showed a generally higher tendency to produce fragmented extrudate, especially at low water contents (1), which is why a formulation with 20% Avicel PH 101 + 80% lactose could not be spheronized equally successfully on the NICA unit as on the Alexanderwerk unit.

The formulation of fenoldopam and succinic acid showed a good extrusion and spheronization behavior for all extruders, despite its low Avicel PH content. Because the poorly soluble drug and acid bound the liquid more effectively in the formulation than did the soluble sugars, no water movement was observed even at higher extrusion pressures. The higher pressure again resulted in a more intense densification of the mass, and the water content was less critical for the extrusion on the Gabler unit (ranging from 31 to 34%) than for the other two types of extruders.

The formulations with Avicel CL/RC showed a different behavior during spheronization, transforming gradually from rounded cylinders into dumb-bells and spheroids. These intermediate stages have not been observed as distinct phases for formulations with Avicel PH 101. During longer spheronization times (>10 min), the material became quite hot and tended to adhere to the spheronizer wall and to decompose under the exposed heat, turning a brownish color, and generating an odor of burned sugar. The resulting spheroids were very hard and generally of inferior sphericity than comparable Avicel PH 101 pellets. The elastic rather than plastic properties of the extrudate opposed the rounding of cylinders into spheres during spheronization, as described by O'Connor (5). For the colloidal grades of Avicel the influence of the formulation overrode the influence of extrusion pressure and thus the type of

extruder used. All formulations resulted in pellets at the same water content, with a tendency to larger pellets than the targeted 710–1250 μm fraction. This was caused by the higher swelling properties of Avicel CL/RC as compared to Avicel PH on leaving the die of the extruder.

The few batches run on a ram extruder for comparison showed that the ram usually resulted in pellets larger than 1 mm, despite the 1 mm die that was used for these trials. The composition and water contents needed for successful spheronization were more critical than for any of the other extruders.

Comparison of Pellet Size and Percent Yield Between 710 and 1250 μm

The mean particle size by weight characterized the size of the pellets of different batches and proved to be a good tool for the comparison of the three extruder types. To determine whether the observed differences in the spheronization behavior expressed themselves in significant differences in the mean particle size of weight and the percent yield between 710 and 1250 μm, those values were tested by a two-way ANOVA without replicates at the 95% significance level. For significant ANOVA tests, a test on the least significant differences (LSD) was conducted for each extruder to determine which of the extruders differed significantly. All batches with 100% > 2000 μm were not differentiated any further, but treated as batches with a mean particle size of 2000 μm and a yield of 0% for the 710–1250 μm fraction.

Table 1 shows that both parameters, the mean particle size and the yield of the 710–1250 μm fraction, are significantly different. For the three extruders, however, only the Alexanderwerk/Gabler and the NICA/Gabler interactions were significant for the mean particle size. The Alexanderwerk and the NICA extruders did not produce significantly larger or smaller pellets for any of the different formulations, for formulations with not even low water content as demonstrated in Table 1. The percent yield differed significantly only for the Alexanderwerk extruder and the Gabler extruder, and the NICA/Gabler interaction was only significant at the 90% level for the percent yield.

The mean particle sizes obtained for different formulations and water contents are depicted in Fig. 1. The cylinder extruder and the radial-screw extruder both showed a similar behavior for all the investigated formulations, with an increasing mean particle size for all formulations as the water content increased. For an identical water content, the mean particle size was similar for both extruders and the required water content for either small or large pellets increased with increasing amounts of Avicel PH 101 in the formulation. Regression lines of the particle sizes against the water content were parallel for the Avicel PH 101 and the lactose + Avicel PH 101 (80 + 20 and 50 + 50, respectively) formulations. Similar regression lines for the fenoldopam, mannitol, and the lactose + Avicel PH 101 (75 + 25) formulations had different slopes. Because the particle size for the NICA unit was less influenced by the water content at lower water levels than at higher levels, the NICA extruder showed a generally less linear relationship than the Alexanderwerk unit between the mean particle size and the water content of formulations. Testing the slopes for significant differences by a paired *t*-test for all formulations indicated that there

Table 1

Significant Differences in the Mean Particle Size of Weight and the Percent Yield, When Using the Alexanderwerk (A), the Gabler (G), or the NICA (N) Extruders

Testing of Significant Differences Between Extruders	*F* Value for Two-Way ANOVA ($p < 0.05$) $F_{critical}$ (2; 30 df) = 3.32	*t* Value for LSD test ($p < 0.05$) $t_{critical}$ (28 df) = 2.04		
		A/N	A/G	G/N
Mean particle size of weight in μm	8.75[a]	1.23	4.08[a]	2.85[a]
Yield of 710–1250 μm fraction in %	4.37[a]	0.90	2.89[a]	1.99*
Mean particle size of weight in μm for low water contents	0.97			
t-test for paired samples for A/N			t (A/N) = 0.97 $t_{critical}$ (7 df) = 2.37	
Yield of 710–1250 μm fraction in % for low water contents	0.69			
t-test for paired samples for A/N			t (A/N) = 0.69 $t_{critical}$ (7 df) = 2.37	

[a]Significant test results.
df = Degrees of freedom.
*Significant at 90% level only.

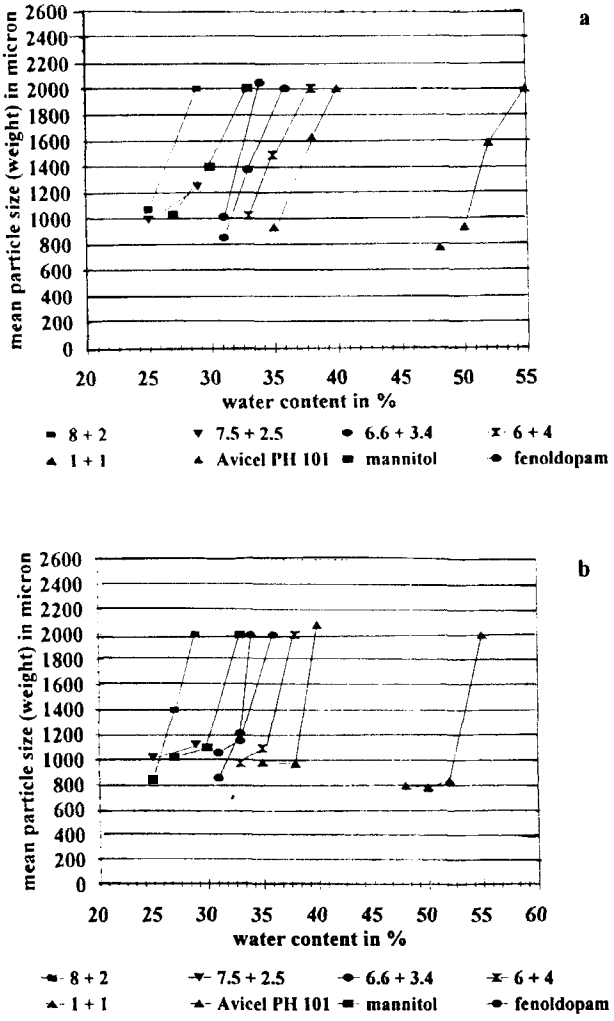

Figure 1. Comparison of the mean particle size of weight at different water contents for different formulations extruded with the (a) Alexanderwerk rotary-cylinder extruder, and (b) NICA radial-screw extruder.

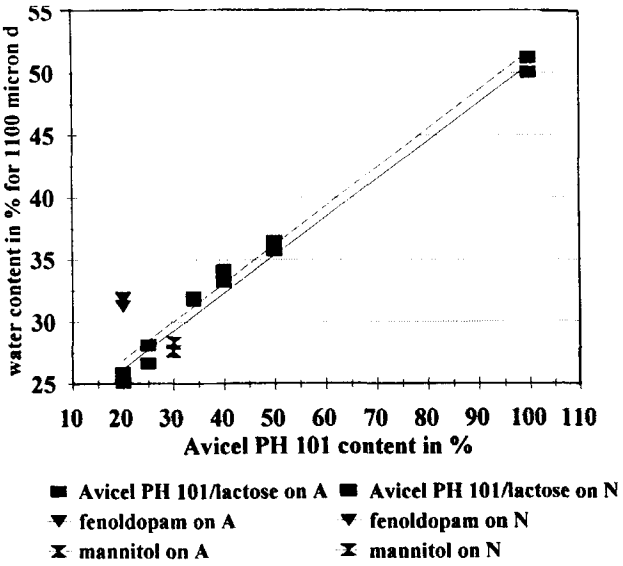

Figure 2. Linear relationship between the amount of water in percent required for a mean particle size (d) of 1100 μm and the content of Avicel PH 101 (in percent) in the formulation for the Alexanderwerk (A) and the NICA (N) extruder; correlation coefficient of regression lines = 0.99.

were no significant differences for the slopes of regression lines between the two extruders. The two extruders were thus not significantly different for the investigated formulations.

When the theoretical water content for a mean particle size of 1100 μm for each formulation and extruder was calculated from the slope of the regression lines, an only slightly higher water content was required for the NICA unit than for the Alexanderwerk unit. A plot of the water content against the content of Avicel PH 101 for each formulation in Fig. 2 resulted in a linear correlation for the Avicel PH 101 and the Avicel + lactose formulations with a good correlation coefficient for both extruders (0.99). The slopes were 0.31 for both extruders. Intercepts were 20.1 for the Alexanderwerk and 20.8 for the NICA units. The water content required for a desired mean particle size could thus be calculated for any Avicel PH 101 + lactose formulation for processing on each extruder on the basis of the slopes and the intercepts of these linear relationships. The 70% mannitol formulation did not differ very much from these regression lines but other formulations such as the fenoldopam + succinic acid formulation did not fit.

The axial, single-screw extruder in Fig. 3 behaved completely differently from the other two types, resulting in almost horizontal lines for each of the formulations over a wide range of water contents. Only for formulations with 80% of lactose did the mean particle size show a strong, but inconsistent dependence on the water content.

Basically the same differences were also found for the three extruders, when comparing the yield of 710–1250 μm pellets, which indicates the width of the particle size distribution within a batch. The Alexanderwerk and the NICA units behaved quite similarly resulting in comparable yields for the same formulations, and the Gabler unit resulted in significantly higher or lower yields depending on the individual formulation. This coincides with the decreasing dependence of particle size

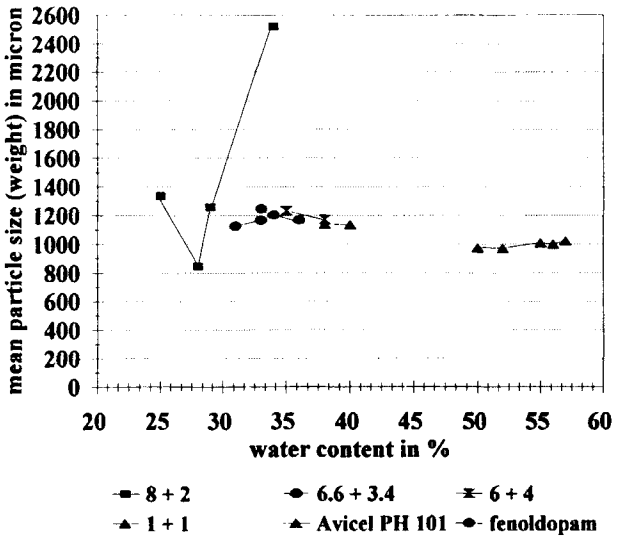

Figure 3. Mean particle sizes plotted against the water content of different formulations, extruded with a Gabler single-screw extruder.

on the water content in the direction Alexanderwerk > NICA > Gabler extruder.

The investigated fenoldopam + succinic acid (1 + 1) formulations showed only very little dependence on the type of extruder used, and were therefore considered as quite robust formulations, suitable for extrusion–spheronization, with little tendency of water movement.

Bulk Density, Hausner Factor, and True Density

The determination of pellet density was performed to determine whether the different compression forces exerted by the different types of extruders manifest themselves in a different density of the product. Instead of using the unsieved pellet batches, only the 710–1250 μm cut was used for the determination of bulk density and true density. This was carried out to eliminate differences caused by the different size of pellets for individual batches. A one-way ANOVA test (Table 2) was conducted for both types of density to compare the overall differences between the three extruders. In addition, a one-way ANOVA was done for each group of formulations separately. An LSD test for significant ANOVA tests showed which of the three extruders actually caused significantly different density values.

When all batches produced by each of the extruders were compared, the Gabler and Alexanderwerk batches showed a significantly higher bulk density than batches produced by the NICA extruder. Figure 4 shows the mean values and the variance for the bulk density of pellets produced by the different extruders. As already demonstrated by the statistical tests, there were no real

Table 2

Differences in the Bulk Density and the True Density for the Alexanderwerk (A), the NICA (N), and the Gabler (G) Extruder; F Values for One-Way ANOVA and t Values for the LSD Test Among Individual Extruders for Significant ANOVA

	F Value for df and 95% Significance	LSD Test *t* Value for df and 95% Significance
Bulk density in cm^3/g for all batches together	F (2;56) = 6.59[a] $F_{critical}$ = 3.2	A/G: 0.024 $t_{critical}$ (56) = 0.028 A/N: 0.047[a] $t_{critical}$ (56) = 0.031 G/N: 0.071[a] $t_{critical}$ (56) = 0.027
True density in cm^3/g for all batches together	F (2;37) = 0.032 $F_{critical}$ = 3.20	
True density in cm^3/g for Avicel PH 101 + lactose pellets	F (2;6) = 3.16 $F_{critical}$ = 5.14	
True density in cm^3/g for Avicel PH 101 pellets	F (2;13) = 4.21[a] $F_{critical}$ = 3.81	A/G: 0.027 $t_{critical}$ (13) = 0.031 A/N: 0.005* $t_{critical}$ (13) = 0.032 G/N: 0.032[a] $t_{critical}$ (13) = 0.025
True density in cm^3/g for Avicel PH 101 + mannitol pellets	F (2;4) = 1.83 $F_{critical}$ = 6.94	
True density in cm^3/g for fenoldopam + succinic acid + Avicel PH 101 pellets	F (2;3) = 0.58 $F_{critical}$ = 9.55	

[a]Significant values.
*Significant on 90% level only.

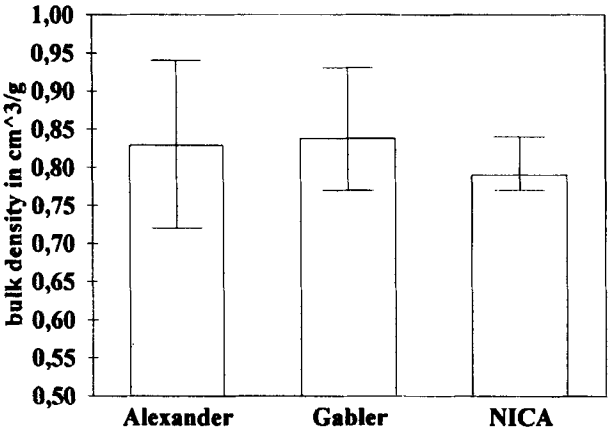

Figure 4. The dependence of the bulk density of pellets on the type of extruder used; Alexander rotary-cylinder extruder (n = 16); Gabler axial, single-screw extruder (n = 26); and NICA radial-screw extruder (n = 17).

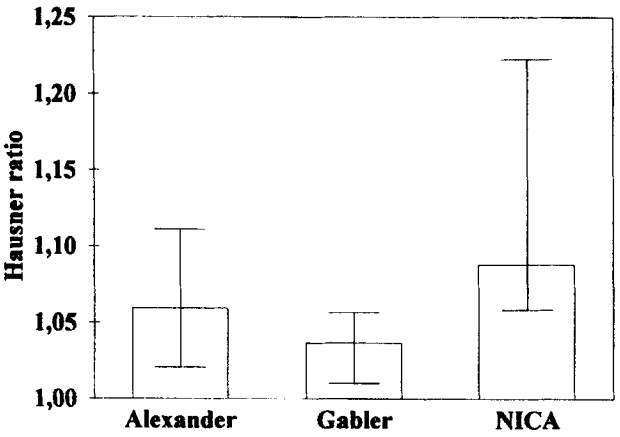

Figure 5. Comparison of the mean values and the variance of the Hausner factor for pellets produced by the Alexanderwerk (n = 16), the NICA (n = 17), and the Gabler (n = 27) extruder.

differences between pellets produced by either a rotary cylinder extruder or an axial, single-screw extruder; the NICA unit produced pellets with a lower bulk density.

There could be several reasons for the bulk density differences. Bulk density is determined by pouring the pellets into a cylinder without any densification and taking the volume they occupy in this cylinder for the calculation of the bulk density as cm^3/g. Flow properties and tightness of packing strongly influence the bulk density. A higher bulk density could thus result from more spherical-shaped pellets that flow and fill the cylinder more easily than do irregular-shaped, less spherical particles. Conversely, a certain amount of fines that pack into the voids left between the spheres would also increase the bulk density for those batches with a higher percentage of smaller pellets and thus a wider size distribution within the investigated 710–1250 μm fraction.

The Hausner factor is defined as the quotient between the bulk density and the tapped density, and should ideally be 1.0 to exhibit good flowability and thus also good packing properties.

Figure 5 illustrates the same relationship as for the bulk density, which is also backed by statistics (significant one-way ANOVA and significant LSD test for Alexanderwerk/NICA and Gabler/NICA). While there is no significant difference between the Alexanderwerk extruder and the Gabler extruder, the NICA extruder differed significantly from both, showing a higher value for the Hausner factor and a much higher batch-to-batch variability than the others. The determination of the Hausner factor is usually done to indicate the change in the volume of bulk materials that takes place because of vibrations during tableting or capsule filling. Because these filling procedures are based on volume rather than weight, this change should be minimal, to ensure a high content uniformity of individual doses. All the Alexanderwerk and Gabler batches showed a Hausner factor close to 1.0, when the 710–1250 μm yield was considered, indicating good flowability and packing properties resulting from spherical pellets.

The NICA extruder, however, resulted in significantly ($p < 0.05$) higher ratios than the Alexanderwerk and Gabler extruders. This is a consequence of the lower bulk density observed for the NICA batches. These pellets have essentially the same size with a rather narrow size distribution of 500 μm, comparable to the batches produced by either of the other extruders. The higher volumes obtained for the NICA extruder after the pellets were poured into the cylinder were therefore reduced more drastically during the 1250 stamps produced in the stamp volumeter, which resulted in larger values for the Hausner factor. This is usually observed for materials with poor flowability and strengthens the suggested idea of a lower sphericity of these batches, even though such lower sphericity was not readily visible. Hellen (6) showed excellent sphericity for the pellets in her work, and such an inferior sphericity of pellets might be caused by the increased tendency of this extruder to produce fragmented extrudates when operated with the punched screen. Therefore, the profile or drilled screens offered by the manufacturer might have been much more suitable for the investigated batches.

Shah (7) demonstrated the decrease in extrusion force for increasing water contents of 50% Avicel PH + 50% lactose mixtures, using an instrumented axial-screw extruder. He initially also expected a decrease in the bulk density at higher water levels because of the reduced compacting at lower extrusion forces. Instead, he found an increase in bulk density at higher water levels, and attributed it to the higher densification from the improved rheological properties of the wetter material.

The determination of the true density provides more information about the volume of voids within the spheres and can therefore be used for a better evaluation of the extent of densification that took place during extrusion and spheronization. Comparing the true densities of different formulations, we detected that the influence of the amount of lactose in the formulations became apparent. Formulations with high amounts of lactose resulted in a higher true density for all extruders than did formulations with small amounts of lactose or no lactose. The higher amounts of lactose seemed to be compacted with fewer voids left in the interior of the spheres because of lactose's partial solution and binding properties during the process. This was more strongly expressed at higher water contents, in which more lactose was dissolved in the paste than for lower water contents. True density thus decreased with decreasing amounts of the soluble lactose and for identical formulations with decreasing amounts of water. Even though this was not statistically significant, because of the limited number of samples for each factor, the tendency is quite visible from the graph in Fig. 6. The water content, however, not only influenced the density of formulations with soluble components, but also the density of formulations that contained only Avicel PH 101 (Fig. 6).

From Table 2, no significant differences between the different extruders could be observed when the true densities of all the batches were compared. Only when differentiating between the individual classes of formulations using a two-way ANOVA test did the true density result in lower values for the NICA extruder as compared to the Gabler extruder. This was, however, significant only for the binary Avicel PH 101 + water formulations and only for the NICA/Gabler interaction; the Alexanderwerk/NICA interaction was significant only at the 90% level. Therefore, the extrusion forces applied to the mass by the different extruders determined the true density only for Avicel PH 101 pellets, which showed a generally lower density than the lactose + Avicel PH pellets because of the lack of binding properties of soluble components.

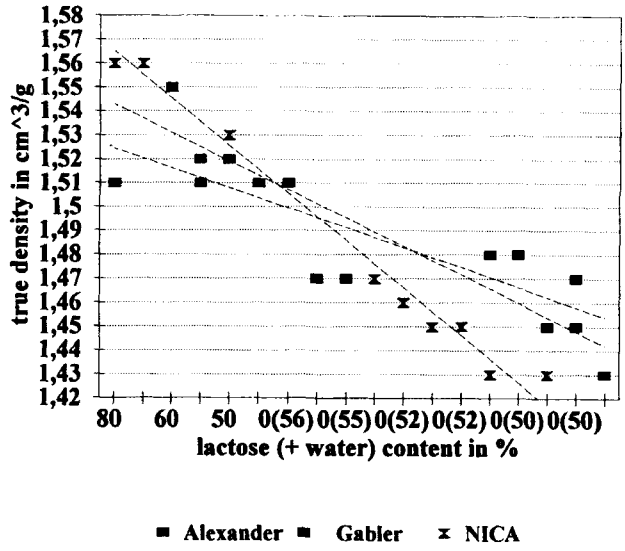

Figure 6. The dependence of the true density of pellets (mean of $n = 3$, SD < 0.01) on the composition and the water content of formulations; Avicel PH 101 ± lactose + water formulations (water contents are given as percent values in brackets).

Friability

The friability of all pellet batches produced by either the cylinder or the axial-screw extruder showed a similar value of less than 1% for all of the investigated placebo mixtures in Fig. 7. There were no statistically significant differences (t value for paired t-test = 0.22; $t_{critical}$ for 16 degrees of freedom [df] = 2.12). No tests were carried out for the NICA batches, but because

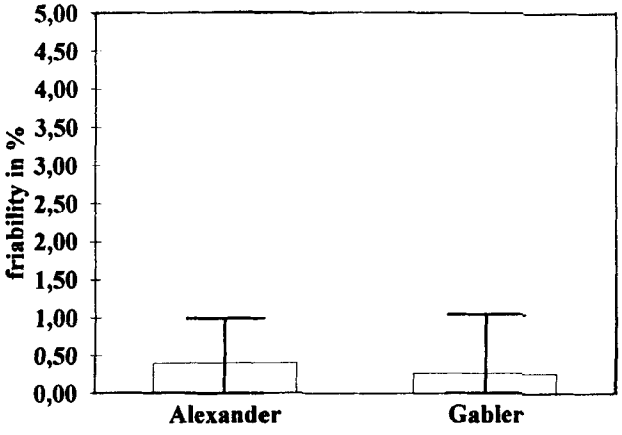

Figure 7. Comparison of the mean values and the variance of friability in percent for all pellet formulations produced by the Alexanderwerk ($n = 26$) or the Gabler ($n = 12$) extruder.

handling procedures showed no differences in the behavior for those batches, no significantly different friability was expected for them either. Nor could any connection between the friability of pellets and the composition of formulations be detected. The altogether quite low friability of all of these pellets therefore has to be attributed to the extrusion–spheronization process itself, which achieves a much higher compacting of materials than other pelletization techniques, for which much higher friability values have been reported in the literature (8).

CONCLUSIONS

Despite the partially different quality of extrudates, the Alexanderwerk extruder and the NICA extruder produced almost identical spheres on the basis of their mean particle size and particle size distribution for all of the investigated formulations. The Gabler extruder showed a different behavior in its dependence of the mean particle size of pellets on the water content and Avicel PH 101 content of formulations. The incidence of an extremely rough or even shark-skinned extrudate alone did not determine the quality of pellets; good pellets could be produced from rough or smooth extrudates alike, given extrudates were not fragmented excessively but were still cylindrical. The success of spheronization of extrudates into pellets with the desired yield therefore depended on the right composition of the formulation, the water content of formulations, and the type of extrusion. While being similar in their water content and mean particle size dependency, the NICA and the Alexanderwerk extruders differed significantly in the density of spheres. Both true density and bulk density were significantly higher for the Gabler or the Alexanderwerk extruders than for the NICA extruder. The Alexanderwerk gravity-feed extruder therefore combines low-pressure extrusion with low heat buildup and minimal water movement with the high densification usually observed for high pressure extrusion. This makes it a good tool for many applications, even though the tedious cleaning procedure of the countless holes of the die cylinder has to be regarded as a drawback of this equipment.

In conclusion, one has to consider not only the spheronization process and its processing parameters when evaluating the pelletization of a new formulation, but also the extrusion method. Even though the extrusion parameters have mostly proved to be noncritical for the resulting sphere quality (9), the extrusion method itself exhibits a strong influence on both pellet size and physical pellet properties and should therefore be taken into consideration when choosing the extrusion equipment for a pellet formulation.

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