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Evaluation of a Conical Mill for Screening of Direct Compression Formulations

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ABSTRACT

Suitability of a Quadro Comil™ for screening of direct compression tablet masses was evaluated with respect to alteration of particle size distribution and blending efficiency. Air jet sieving was qualified for determination of a particle size of spray-dried lactose and microcrystalline cellulose. Using a full $3^1 \times 2^3$ factorial design not only effects of single processing parameters (output screen size, impeller shape, velocity of the mill, and type of powder), but also their respective combinations were investigated in terms of impact on particle size and flow properties (angle of repose, bulk and tapped densities). Particle sizes before and after passing the Comil were found to be normally distributed. The results indicate that the process does not allow any of the powder characteristics studied beyond normal batch-to-batch variability. This refers in particular to the proportion of fines. For evaluation of the deagglomeration effectiveness, a 2^3 design was implemented with iron oxide as a model drug. Homogeneity of the blends was determined optically, and after screening twice it was found to be acceptable even with this substance, which has a particularly high agglomeration tendency, high density, and small particle size. The Quadro Comil is therefore regarded as fully suitable for deagglomeration of powders in a gentle and effective manner.

Dedicated to Professor Dr. K. H. Bauer on the occasion of his 65th birthday.

INTRODUCTION

Direct compression (DC) is an efficient method of tablet manufacture as it saves time and energy, is environmentally friendly, and reduces investment on buildings and equipment since it requires fewer process steps compared to traditional granulation methods. Conformance to good manufacturing practice (GMP) can be attained more easily if all manufacturing steps are carried out in closed containers. This has the advantage of avoiding dust and powder leakage, thereby protecting operators and the environment from potent drugs. The direct compression process is a standard production technique (United States Pharmacopoeia, 1995) which is particularly suitable for products sensitive to water and raised temperature.

Blending and screening are the main unit operations involved in manufacture of DC formulations, both operations being necessary in order to gain homogeneous mixtures within tight coefficients of variation (approx. 2%). In contrast to mixing alone, the screening step is regarded as able to destroy agglomerates in the blend by providing more shear stress. The geometry of the machine as well as process variables such as speed of the mixer, total time, etc., are of major importance for reproducible results and validation of the unit operations.

The conical mill (Quadro Comil) meets the requirements for GMP production, can be used continuously with different feeder systems, and is easy to clean after use. Additionally, different sizes of the machine for various throughput levels are available, which should be advantageous for scale-up. As the impeller does not touch the rigid screen, which is made of 2-mm steel sheet (Fig. 1), there is no danger of contamination of the product by broken screens or metal abrasion. The use of the Comil has already been described in detail in the literature for comminution of a commercially available granulation (1,2) and for improving color uniformity (3) as well as content uniformity (4) of tablets produced by direct compression. As no statistically validated data are available on processing of excipients commonly used for DC with the Comil, a need for a corresponding investigation is apparent.

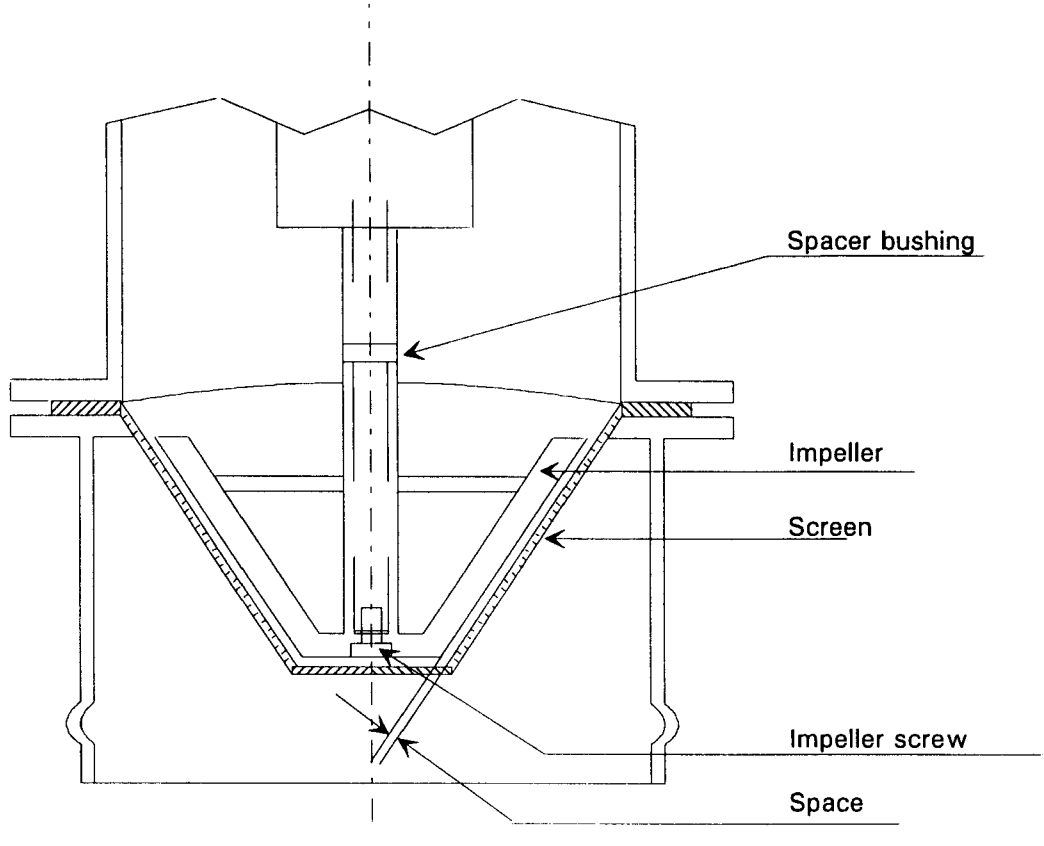


Figure 1. Sectional drawing of the Quadro Comil.

MATERIALS AND METHODS

A Quadro Comil model 194 S (Quadro Process INC, St. Jacob's, Ontario, Canada) was used to screen spray-dried lactose [Lactose DC 11, batch numbers 3843777 (= batch1), 4708928 (= batch2), and 9037238 (= batch3); DMV, Veghel, Holland] and microcrystalline cellulose (AVICEL PH102, batch number 7634396, FMC Corp., Philadelphia, USA).

The raw materials were characterized before and after screening through the Comil with regard to their particle size distribution by air jet sieving (Alpine AG, type 200 LS, Augsburg, Germany), using standard certified sieves of mesh sizes 40 μm, 63 μm, 100 μm, and 125 μm. The material was subjected to sieve analysis with these sieves for 5 min, and with a 200 μm sieve for 2 min at a fixed pressure of 3 to 5 kPa. For each determination (on each sieve), about 10 g of the material (weighed accurately on a balance with a reading of 10 mg) was sieved in the presence of a small amount of highly dispersed Al_2O_3 in order to avoid electrostatic effects. Residues of material on the sieves were weighed to the same accuracy as before. Evaluation of the particle size distributions was made by calculating the normal probabilities of % oversize and linear regression when plotted as a function of sieve sizes using MS Excel 4.0 (Microsoft Corp., Redmont, WA, USA) and Origin 3.5 (Microcal Software Inc., Northampton, MA, USA).

True particle densities were determined using a Multivolume Pycnometer 1305 (Micromeritics S.A., Zaventem, Belgium) with helium as a flush gas.

Poured and tapped densities were determined according to USP 23. The device was equipped with a height sensor (Ciba Geigy, Switzerland) for automatic analysis.

Flow properties were assessed as follows: A small sample of the powder is placed on a sample holder made of stainless steel in the form of a quarter cylinder segment. It is slowly tilted from the horizontal. The angle of repose is registered when powder falls from the sample holder onto the balance (Ciba Geigy Ltd., Basle).

Preliminary Tests

The conical screening mill was used with different screens (apertures of 12.7 mm, 9.5 mm, 4.75 mm, 1.9 mm, and 1.57 mm in diameter; listed in Table 1) and one type of impeller (2C-1601-001 round). A small gap between the impeller and the screen was always maintained using the corresponding spacer bushings (see Table 1 and Fig. 1).

Samples of sizes of 0.5, 1, and 3 kg were fed in by hand. The mill was operated at two speeds (500 and 1500 rpm), which were adjusted on the empty running mill using a stroboscope prior to feeding the samples. The experiments were done in random order.

Final Experiments

Final tests were done on the basis of a statistically optimized experimental design in order to estimate the effects of single parameters as well as their interactions. For this STAVEX software, an expert system for statistical trial plans (Ciba Geigy Ltd., Basle, Switzerland), was used. The system suggested a full $3^1 \times 2^3$ factorial design which was attained with 24 experiments: 3 speeds (600, 1000, and 1400 rpm), 2 materials with 1 kg in each run (Lactose, Avicel), 2 impellers (2C-1601-001 round and 2C-1609-051 square), and the 2 smallest screens for most effective "grinding" (2C 062 R 050 41

Table 1

Screen, Impeller, and Spacer Bushing Specifications

Type Screen	Shape of Holes	β (mm)	Open Space (%)	Impeller: Round, 2C-1601-001, Used with Bushing Size (in.)	Impeller: Square, 2C-1609-051, Used with Bushing Size (in.)
a. 2C-500 Q 050 64	Square	12.7	64	0.250	0.225
b. 2C-375 Q 050 63	Square	9.5	63	0.200	0.225
c. 2C-187 Q 050 42	Square	4.75	42	0.175	0.225
d. 2C-075 R 050 51	Round	1.9	51	0.200	0.175
e. 2C-062 R 050 41	Round	1.57	41	0.200	0.175
f. 2C-018 R 015 30	Round	0.457	30	0.225	0.175

and 2C 018 R 015 30). Again the experiments were performed in random order and analysis of the processed material was done as described above.

For evaluation of the screening efficiency lactose (1 kg for each determination) was blended with 1% iron oxide red pigment (batch number 8829625, Colorcon Ltd, Orpington, U.K.) as a model substance. Preblends were made on a Turbula blender type T2C, container size 2 liters; degree of filling 50–75% (Bachofen Maschinenfabrik, Basle, Switzerland) for 20 min at 42 rpm. In order to determine parameters affecting the deagglomeration efficiency, another experimental design suggested by STAVEX was used: 2 impellers, 2 screens, 2 speeds of 600 and 1400 rpm (Table 7). The final blends were made as described above. Samples of the powder blend were spread out on white paper using a spatula and the presence of red spots or stripes was assessed optically (5).

RESULTS AND DISCUSSION

Evaluation of the Sieving Method: Unprocessed Materials

The reproducibility of air jet sieving for the determination of particle size distribution was initially assessed. Spray-dried lactose (Lactose DC 11) was chosen as a commonly used and commercially available excipient. Results of the determination of the residues on the sieves after air jet sieving are listed in Table 2A (first section—batch 1). The confidence intervals of 10 repeated determinations on each sieve were found to be less than 1.4% of the total sieved material, i.e., approx. 0.14 g in all cases. All the confidence intervals were of the same magnitude, being highest with medium-sized sieves. Regarding the variation coefficients, an increase with increasing mesh openings of the sieves is obvious. This is due to the total amount of material remaining on the sieves, which is small on the larger sieves (e.g., between 0.10 and 0.23 g on the 200-μm sieve).

The material remaining on larger sieves consists of only a small number of large particles, probably aggregates. The destruction of such particles by mechanical stress during the sieving process would possibly alter the result markedly.

The sieving procedure was repeated on another 2 batches of spray-dried lactose from the same supplier. Each experiment was again done 10 times; the results given in Table 2A (sections 2 and 3) are also expressed as residues on the respective sieves, confidence intervals, and variation coefficients. Again the same magnitudes of confidence intervals were found ($\alpha = 5\%$). The sieving procedure with lactose was also performed with 1 batch of microcrystalline cellulose and each determi-

Table 2A

Air Jet Sieving Method: Confidence Interval of Repeated Measurements with Lactose DC 11

	Sieve Sizes				
Lactose	200 μm	125 μm	100 μm	63 μm	40 μm
Batch 1					
$\bar{x}$ ($n = 10$)					
Residue on sieve (%)	1.5	31.5	51.6	78.2	90.1
Conf. interval	±0.29	±1.31	±1.39	±0.74	±0.52
Var. coeff.	26.6	5.7	3.7	1.3	0.8
Batch 2					
$\bar{x}$ ($n = 10$)					
Residue on sieve (%)	1.3	27.0	46.5	76.3	91.2
Conf. interval	±0.19	±0.96	±0.78	±0.50	±0.20
Var. coeff.	20.1	4.9	2.3	0.9	0.3
Batch 3					
$\bar{x}$ ($n=10$)					
Residue on sieve (%)	3.0	35.4	53.7	78.7	90.8
Conf. interval	±0.44	±0.67	±0.63	±0.29	±0.33
Var. coeff.	20.2	2.6	1.6	0.5	0.5

Legend. var. coeff.; variation coefficient (%); conf. interval, confidence interval of the mean, $\alpha = 5\%$.

nation repeated 5 times (Table 2B). The variation coefficient on each sieve in the repeated experiments was in the same range as was found with Lactose DC11 (α = 5%). The only exception was the significantly lower variation coefficient on the 200-μm sieve. From these results it was concluded that the repeatability of the air jet sieving method is suitable for particle size analysis of the materials under investigation.

From the summarized results given in Table 3, the three different batches of lactose can be compared: For each of the given mesh sizes of the sieves the differences of the material remaining on each sieve were found to be statistically significant for the three batches. The only exception was the 200-μm sieve, which is regarded as less meaningful for the above-mentioned reasons. The absolute difference was greatest on all sieves between batch 2 and batch 3 except for the 40-μm sieve, where the greatest difference was between batch 1 and 2.

For better comparison of particle size distributions, model distributions are usually fitted to the data. Milled granules, including lactose granules, could serve as an example for the present material. They do not usually show log-normal distribution (6) but rather follow the Weibull function. For materials showing frequent deviations from both distributions, Motzi et al. (7) have introduced another weighted linear regression technique

Table 2B

Air Jet Sieving Method: Confidence Interval of Repeated Measurements of Microcrystalline Cellulose

	Sieve Sizes				
Avicel	200 μm	125 μm	100 μm	63 μm	40 μm
$\bar{x}$ (n = 5)					
Residue on sieve (%)	8.2	37.1	49.2	70.0	83.0
Conf. interval	±0.58	±1.54	±0.90	±0.64	±0.48
Var. coeff.	6.2	3.6	1.6	0.8	0.5

Note. See legend to Table 2A.

Table 3

Summary of Characteristics of Unprocessed Lactose DC11 and Avicel

	Lactose				
	Batch 1 (n = 10)	Batch 2 (n = 10)	Batch 3 (n = 10)	Mean	Avicel
True particle density (g/cm^3), n=10				1.544	1.572
Poured density (g/cm^3), n=10				0.647	0.354
Tapped density (g/cm^3), n=10				0.748	0.423
Hausner ratio				1.157	1.196
Angle of repose				45°	46°
Particle Size Distrib. Fit					
Slope	-0.0215	-0.0222	-0.0199	-0.0212	-0.0144
Confidence interval	±0.00040	±0.00038	±0.00049		±0.00018
Variation coefficient	2.6	2.4	3.4		1.7
Mean particle size (μm)	100.0	97.6	105.2	100.9	102.0
Confidence interval	±1.5	±0.66	±0.82		±1.1
Variation coefficient	2.13	0.94	1.09		1.49
Minimum correlation coefficient	>0.997	>0.998	>0.998		>0.998

based on the log-normal distribution. On the other hand, milled materials such as ammonium sulfate treated in a hammer mill have previously been reported to be normally distributed (8).

The particle size distributions under investigation were found to be normally distributed, with correlation coefficients being better than 0.999 in most cases, and always better than 0.99. Figure 2 shows normal probability plots of percentage oversize of lactose batch 1 and of microcrystalline cellulose. Table 3 compares the results of curve fitting of standardized normal distributions of three batches of lactose and of microcrystalline cellulose.

Comparison of the three batches of lactose in terms of mean particle size shows significant differences between all the batches, the difference between batches 2 and 3 being the greatest. This is in accordance with the results of the raw data (see above). The slope of the normal probability plot is a measure of the width of the particle size distribution. No significant difference was found between the batches in this respect (Table 3) nor with the intercept (data not shown).

In Table 3 corresponding results for microcrystalline cellulose are listed. According to the slopes of fitted normal distributions, Avicel has a broader particle size distribution than is the case with Lactose DC11, whereas the mean particle size is very similar.

Additional characteristics of Lactose DC11 and Avicel are also compared in Table 3: The true particle densities were found to be very similar whereas poured and tapped densities differ widely. Angles of repose were practically identical.

For DC purposes narrow size distributions should be preferable in order to prevent manufacturing problems due to wide batch-to-batch variabilities. The following experiments were therefore focused on spray-dried lactose rather than Avicel. Another reason for this is its fragility: Processing could possibly result in a higher proportion of fines, which would give rise to flow problems and poor tabletability, a critical behavior which should be checked prior to any formulation work.

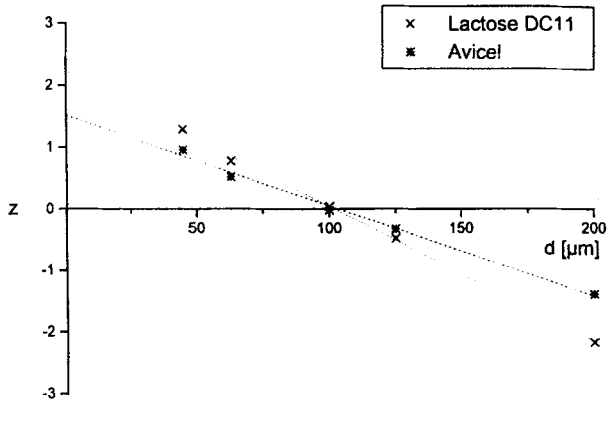


Figure 2. Normal probability plot of percentage oversize of raw batches of Lactose DC 11 and Avicel PH102.

Preliminary Experiments: Effect of Processing on Particle Size

From the experiments of Motzi et al. (2), who comminuted granules, it can be expected that the Comil would produce reproducible size distributions. In contrast to their study, processing in our case should preferably *not* grind DC materials. The experiments were done with batch 1 of Lactose DC11 using 1 impeller, 5 different screens, 2 speeds of revolution, and 3 sample sizes for processing (for exact conditions, see Table 4).

Comparison of raw data of unprocessed lactose batch 1 (Table 2) and processed material (Table 4) surprisingly showed an increase in particle size: The fractions on the relevant sieves (125, 100, and 63 µm) was significantly greater after processing ($\alpha = 5\%$). This increase, however, was minor and the spreads were overlapping. Also, after passing the Comil, size distributions of the material were found to be Gaussian ($r > 0.998$ in all cases). When comparing mean particle sizes calculated from the Gaussian fit (Tables 3 and 4), the increase in particle size by processing was also significant ($\alpha = 5\%$), increasing from 100.0 to 104.7 µm. No significant alteration of the width of the size distributions was caused by the processing (slopes of the fitted lines; Tables 3 and 4).

This finding is in contrast to published data: when Fourman et al. (3) compared a size distribution of lactose before and after processing with a Comil, they did not find any great effects. Motzi et al. (1,2), however, found marked comminution when a Comil type 197 was used with a granule of larger particle size (1680–1180 µm) as well as larger mesh sizes of screens (1900 µm and above). The increase in particle size found here with spray-dried lactose may be explained in two ways:

1. Since the sample sizes are 1 kg, segregation of the material can occur during and after processing, which may give rise to systematic errors when subsampling material for sieve analysis. This explanation is regarded as unlikely because all of the samples were taken from different positions within the pile of processed material, all the determinations showed the same trend,

Table 4

Particle Size Effects of Processing: Preliminary Results Using Lactose DC11 (batch 1) and Impeller 2C-1601-001 (round)

Run	Screen[a]	rpm	Sample Size (kg)	Residues on Sieves (%) 200 μm	125 μm	100 μm	63 μm	40 μm	Particle Size Distr. Fit Slope	y-50%[c] (μm)
1	a	500	0.5	3.0	36.3	58.2	81.9	92.1	0.02053	108.5
2	b	500	0.5	2.1	33.8	55.6	79.6	91.7	0.02118	104.7
3	c	500	0.5	2.5	32.2	55.1	78.4	90.4	0.02033	103.6
4	d	500	0.5	2.2	34.9	52.4	78.6	90.5	0.02058	103.3
5	e	500	0.5	1.9	32.9	53.6	79.8	91.1	0.0213	103.3
6	a	1500	0.5	2.7	33.2	55.3	79.5	91.7	0.02054	105.4
7	b	1500	0.5	3.0	34.9	57.5	81.5	92.9	0.02077	108.3
8	c	1500	0.5	2.9	35.0	57.7	81.0	91.4	0.02037	107.1
9	d	1500	0.5	2.8	33.7	53.3	81.0	91.9	0.02061	105.9
10	e	1500	0.5	3.2	31.1	52.4	80.2	89.4	0.01961	103.7
11	e	1500	1.0	1.2	36.7	53.9	80.2	91.3	0.02238	103
12	d	1500	1.0	1.4	33.4	55.9	83.3	90.5	0.02226	103.8
13	c	1500	1.0	0.8	33.2	55.2	81.4	92.0	0.02376	102.1
14	e	1500	3.0	0.7	32.9	53.5	80.2	89.7	0.02333	99.6
15	d	1500	3.0	2.0	32.4	53.3	82.4	91.3	0.02151	104.3
$\bar{x}$ (n = 15)				2.2	33.8	54.9	80.6	91.2	0.02102	104.7
Conf. interval[b]				0.43	0.81	0.99	0.72	0.50	0.00065	1.3
Var. coeff.[b]				36.7	4.4	3.3	1.6	1.0	5.5	2.2

[a]Code for screens, see Table 1.
[b]Conf. interval, confidence interval of the mean, α = 5%; var. coeff., variation coefficient (%).
[c]y-50%, mean particle size (μm).

and the confidence intervals of all determinations were not increased compared to the repeated experiments with the unprocessed material (±1.3 and ±1.5; Tables 3 and 4).

2. During processing the material is exposed to compaction between the impeller and the screen to such an extent that cohesion and bonding between the particles of spray-dried lactose becomes possible.

The increase in particle size is affected by the screen size. When the results using screens a and b (runs 1, 2, 6, and 7 in Table 4) are compared to all the other experiments, a significant difference is found regarding the mean particle size: bigger apertures in the screen cause larger particles. This may also be an effect of the square holes in the screen, because when all the results with square screens of the same sample size (runs 1, 2, 3, 6, 7, and 8) are compared, the particle size increase is significant, whereas the fraction of open space of the screen is of less importance.

On the whole, the increase in particle size on processing is significant, but it is of the same magnitude as was found for batch-to-batch variability. From these preliminary experiments it was concluded that the conical mill only altered particle sizes slightly, to an extent which is not significant for the manufacturing process. Therefore the usefulness of the conical mill as a screening machine for DC should be further assessed.

Final Evaluation of the Comil

Table 5 shows the processing parameters for the full $2^3 \times 3^1$ factorial design which was suggested by the STAVEX program. As the preliminary experiments had not hinted at comminution of the material, but at less increased particle sizes with small round screens, only the 2 smallest available screens were chosen for the final experiments. They are also regarded as being most effective for deagglomeration (see below). Other parameters were 2 impellers (round and square), 3 speeds of revolution, and the 2 materials.

Results of all the 24 experiments are listed in Table 5. In accordance with the preliminary experiments it was found that none of the particular conditions led to an

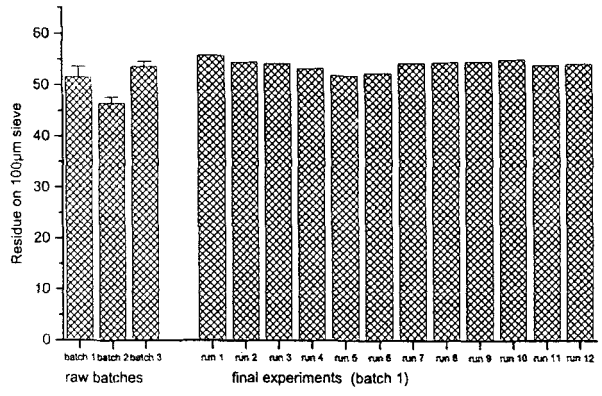


Figure 3. Comparison of particle sizes (residues on the 100-µm sieves) of Lactose DC11 before and after Comil passage.

extraordinary alteration of the residues on the sieves. Figure 3 shows the residues on the 100-µm sieve as an example: the first 3 bars are the mean values of the residues of the 3 raw batches of lactose. The following 12 bars represent the processed material, the values of which are very close and in the same range as the raw materials and of the values of the preliminary experiments (Table 4). The same was found when the fitted particle size distributions were compared. The increase in particle size (compared to unprocessed material, Table 2) is also significant with the final experiments and of the same magnitude as was found in preliminary experiments. In Table 5 the size distributions are also characterized by the 16% value and 84% value which means ± 1 standard deviation from the mean (50%). The Hausner ratio is slightly better after processing, as is the angle of repose.

In order to compare the effect of processing through the Comil on both of the materials under investigation, the spreads of all the respective data (standard deviation of the pooled data for lactose and cellulose) were compared and found to be similar for the two materials (data not shown). In contrast to the findings with spray-dried lactose, processing of Avicel does not lead to an increase in particle size (Tables 2 and 3) when the mean residues on the sieves are regarded. Experiment No. 21 with microcrystalline cellulose (Table 5) is the only one which may exhibit an extraordinary effect on the particle size: The residues on all the sieves are markedly higher compared to the other experiments using Avicel, which would indicate an increase in particle size during processing in the Comil. In contrast to this, no marked effect of the same processing conditions could be observed when using Lactose DC11 (experiment No. 9 in Table 5).

Hausner ratio and angle of repose also indicate poorer bulk properties of Avicel after processing, which again is in contrast to what was found for spray-dried lactose.

The statistical data analysis was done using of STAVEX fitting linear models to the data of the respective conditions, the results of which are given in Tables 6A and 6B.

In most cases the fit of the linear model was very good (correlation coefficients in row 2 of Tables 6A and 6B), but the measured data which are regarded to be most meaningful (residue on sieve 125 µm and the mean particle size calculated from the fitted curve) led to models which were "just acceptable." For all models and in all cases, the model deviations were independent of the level of the factor (data not shown), the only relevant exception being the y-16% value (coarse proportion of the granule from the fitted normal distributions) which was not independent of the factor V (velocity). The same dependence was found for the residue on the 200-µm sieve, which is regarded to be of minor importance (see above). All the model parameters having α values below 0.05 are significant (for clarity, only these are listed in Tables 6A and 6B). Significant effect is always found with the main effect T, which is the test substance. This means that, not unexpectedly, all the parameters under investigation are different for the two substances. The first five columns of Table 6 show the results of the residue fraction on the sieves. The shape of the impeller has a significant effect on the powder fraction remaining on the sieves with small openings (100, 63, and 40 µm): The round impeller leads to a smaller proportion of fines compared to the square impeller, but the effect is not very marked. The residues on the coarser sieves are independent of impeller shape. There are also combined effects of impeller shape plus test substance and output screen plus speed of revolution, respectively, on the 40-µm sieve as an example. The effects of the interactions of processing conditions are of the same magnitude as the effects of single conditions. All the effects are within the range of batch-to-batch variability (Table 2).

Bulk flow properties in terms of angle of repose (last column in Table 6, part 2) are also influenced by the impeller: The round impeller leads to materials with significantly better flow properties than the square impeller.

Poured and tapped densities (columns 1 and 2 in Table 6, part 2) are slightly affected by velocity of the impeller and by the screen used in the Comill, respec-

Table 5

Effects of Processing: Final Experiments

Lactose Exp. No.	I	S	Velocity (rpm)	Residues on Sieve (%) 200 μm	125 μm	100 μm	63 μm	40 mm	Poured Density (g/cm³)	Tapped Density (g/cm³)	Hausner Ratio	Angle of Repos.	Particle Size Distribution Fit y-16%	y-50%	y-84%	Slope
								Lactose								
1	r	f	600	2.2	34.9	55.9	80.0	91.5	0.641	0.741	1.156	40	152.5	105.2	57.9	-0.02101
2	r	f	1000	1.3	33.6	54.6	79.4	91.9	0.649	0.746	1.149	42	147.2	102.8	58.4	-0.02239
3	r	f	1400	2.3	35.6	54.3	80.1	90.0	0.649	0.735	1.132	40	152.9	104.3	55.8	-0.02048
4	s	f	600	2.1	34.1	53.3	80.1	90.9	0.645	0.735	1.140	39	151.3	103.9	56.5	-0.02098
5	s	f	1000	2.0	32.3	51.9	79.6	90.9	0.649	0.746	1.149	44	149.8	102.7	55.6	-0.02111
6	s	f	1400	1.6	30.3	52.4	78.0	90.2	0.667	0.752	1.128	43	147.1	100.6	54.2	-0.02141
7	r	e	600	2.7	34.6	54.4	80.4	90.6	0.645	0.730	1.131	40	154.2	105.2	56.2	-0.02028
8	r	e	1000	2.5	35.8	54.5	81.2	92.9	0.654	0.741	1.133	38	153.9	107.0	60.0	-0.02117
9	r	e	1400	2.7	33.8	54.7	81.3	91.8	0.645	0.735	1.140	38	154.1	106.1	58.1	-0.02072
10	s	e	600	2.7	34.5	55.1	81.2	92.0	0.645	0.725	1.123	44	154.4	106.5	58.6	-0.02074
11	s	e	1000	2.6	33.2	54.0	80.4	91.1	0.654	0.735	1.125	41	153.3	104.9	56.5	-0.02055
12	s	e	1400	2.5	34.7	54.2	82.2	93.0	0.654	0.741	1.133	42	153.6	107.0	60.4	-0.02134
$\bar{x}$ (n = 12)				2.3	34.0	54.1	80.3	91.5	0.650	0.739	1.137	41	152.3	104.8	57.3	-0.02094
								Avicel								
13	r	f	600	8.0	37.8	51.3	71.6	84.0	0.339	0.410	1.210	50	171.2	104.0	36.8	-0.01480
14	r	f	1000	9.4	38.8	51.6	71.0	84.3	0.339	0.417	1.229	50	175.5	105.6	35.7	-0.01423
15	r	f	1400	8.9	36.0	50.9	71.0	83.5	0.339	0.415	1.223	47	172.7	103.4	34.2	-0.01436
16	s	f	600	7.6	38.9	48.5	69.3	83.0	0.336	0.412	1.227	52	169.9	101.6	33.2	-0.01455
17	s	f	1000	7.1	35.2	48.6	68.6	81.9	0.339	0.415	1.223	50	166.8	98.9	31.1	-0.01465
18	s	f	1400	9.2	38.3	49.6	69.9	82.9	0.338	0.415	1.228	53	174.4	103.2	32.1	-0.01397
19	r	e	600	8.0	37.4	50.1	68.5	83.1	0.339	0.419	1.236	49	170.7	101.7	32.6	-0.01440
20	r	e	1000	8.2	38.8	49.3	71.0	84.3	0.333	0.408	1.224	50	171.6	103.8	36.0	-0.01467
21	r	e	1400	9.6	42.1	53.8	74.3	85.9	0.331	0.404	1.222	50	177.9	110.0	42.0	-0.01464
22	s	e	600	7.6	36.3	47.9	69.0	81.8	0.338	0.412	1.222	53	168.6	99.6	30.6	-0.01441
23	s	e	1000	9.2	37.1	50.3	70.1	81.8	0.339	0.410	1.210	53	174.3	102.5	30.7	-0.01385
24	S	E	1400	9.2	38.4	50.4	70.4	82.8	0.339	0.410	1.223	52	174.8	103.7	32.7	-0.1400
$\bar{x}$ (n = 12)				8.5	37.9	50.2	70.4	83.3	0.337	0.413	1.223	51	172.4	103.2	34.0	-0.01436

Note. I, impeller; S, screen (see Table 1).

Table 6

Part 1: STAVEX Evaluation of Sieve Analysis

Fit	y > 200 µm, Very Good, r = 0.9858 Parameter	α	y > 125 µm, Acceptable, r = 0.8142 Parameter	α	y > 100 µm, Good, r = 0.9340 Parameter	α	y > 63 µm, Very Good, r = 0.9880 Parameter	α	y > 40 µm, Very Good, r = 0.9826 Parameter	α
Constants	5.2875	0.0000	35.6000	0.0000	51.8500	0.0000	75.1025	0.0000	87.3875	0.0000
Main effect[a]										
I					-0.8000	0.0007	-0.4583	0.0153	-0.4792	0.0111
S	0.2417	0.0474					0.4750	0.0126		
V	0.3188	0.0348					0.4438	0.0452		
T	-3.1167	0.0000	-1.9875	0.0000	1.9583	0.0000	4.9667	0.0000	4.0625	0.0000
Interactions										
V^2										
I × S					0.4500	0.0453				
I × V										
I × T							0.3833	0.0358	0.4292	0.0199
S × V							0.6937	0.0044	0.5500	0.0158
S × T										
V × T	-0.3938	0.0124			-0.6250	0.0131	-0.4563	0.0403		
Mean model deviation	0.5360						0.7942			

Part 2: STAVEX Evaluation of Granule Properties

Fit	Poured Density, Very Good, r = 0.9997 Parameter	α	Tapped Density, Very Good, r = 0.9996 Parameter	α	Hausner Ratio, Very Good, r = 0.9783 Parameter	α	Angle of Repose, Very Good, r = 0.9518 Parameter	α
Constants	0.4945	0.0000	0.5773	0.0000	1.1803	0.0000	46.000	0.0000
Main effect[a]								
I							1.3333	0.0018
S			-0.0027	0.0159				
V	0.0021	0.0439						
T	0.1562	0.0000	0.1629	0.0000	-0.0433	0.0000	-4.9167	0.0000
Interactions								
V^2								
I × S								
I × V	0.0021	0.0439	0.0031	0.0199				
I × T								
S × V								
S × T								
V × T	0.0028	0.0130						
Mean model deviation	0.0038		0.0047		0.0092		1.6372	

Part 3: STAVEX Evaluation of Fitted Particle Size Distributions

Fit	y-16%, Very Good, r= 0.9770		y-50%, Just Accept., r = 0.8131		y-84%, Very Good, r = 0.9889		Slope, Very Good, r = 0.9893	
	Parameter	α	Parameter	α	Parameter	α	Parameter	α
Constants	161.555	0.0000	103.525	0.0000	45.5000	0.0000	-0.0178	0.0000
Main effect[a]								
I			-1.000	0.0069	-1.3125	0.0036		
S	1.2542	0.0187	0.9083	0.0120				
V								
T	-10.171	0.0000	0.7583	0.0296	11.6875	0.0000	-0.0033	0.0000
Interactions								
V^2								
I × S								
I × V								
I × T					0.9292	0.0254		
S × V			1.0625	0.0153	1.4563	0.0068		
S × T								
V × T	-1.5063	0.0206	-1.0125	0.0196				
Mean model deviation	2.2609		1.5048		1.7840		0.0005	

[a]I, impeller; S, screen; V, velocity (rpm); T, test substance.

tively, whereas the Hausner ratio (column 3 in Table 6, part 2) is not affected by any of the machine settings.

Parameters of the normal distribution fits on the particle size distributions are related to the machine settings as follows: The mean particle size (column 2 in Table 6, part 3) depends on the impeller (the same effect as above with raw data of residues on the smaller sieves; the round impeller leads to larger particles) and on the output screen (finer screen leads to smaller mean particle size—but not to greater residue on the 40-μm sieve!), whereas the slope (= width) of the particle size distribution is not affected at all. The y-16% value (coarse fraction) is also affected by the screen, and the y-84% (proportion of fines) by impeller shape. Combinations of screen and speed yield effect on mean particle sizes and fines (y-84%-values).

All the effects mentioned above are statistically significant but do not alter the properties of the materials to an extent greater than batch-to-batch variability.

Evaluation of Deagglomeration Capabilities

These experiments should prove whether the Comil is effective as a screening machine in terms of deagglomeration capability. The experimental design was chosen using STAVEX: 4 experiments with 2 impellers, 2 screens, and 2 speeds of revolution (Table 7) were suggested and accepted. The smaller screens were chosen again as they provide the best disaggomeration efficiency.

Each run was performed using 1 kg of Lactose DC11 (batch 1), which was mixed with 1% iron oxide red. This pigment is of small particle size (approx. 2 μm diameter), has a high density, and was used in a small proportion, all of which are factors inhibiting good blending characteristics. Preblends were made in a Turbula mixer at 42 rpm for 20 min.

Table 7

Experimental Design for Blending Evaluation

Run	Impeller	Screen[a]	Speed
1	Round	f	600
2	Round	e	1400
3	Square	f	600
4	Square	e	1400
5	Round	f	1400

[a]For screen types, see Table 1.

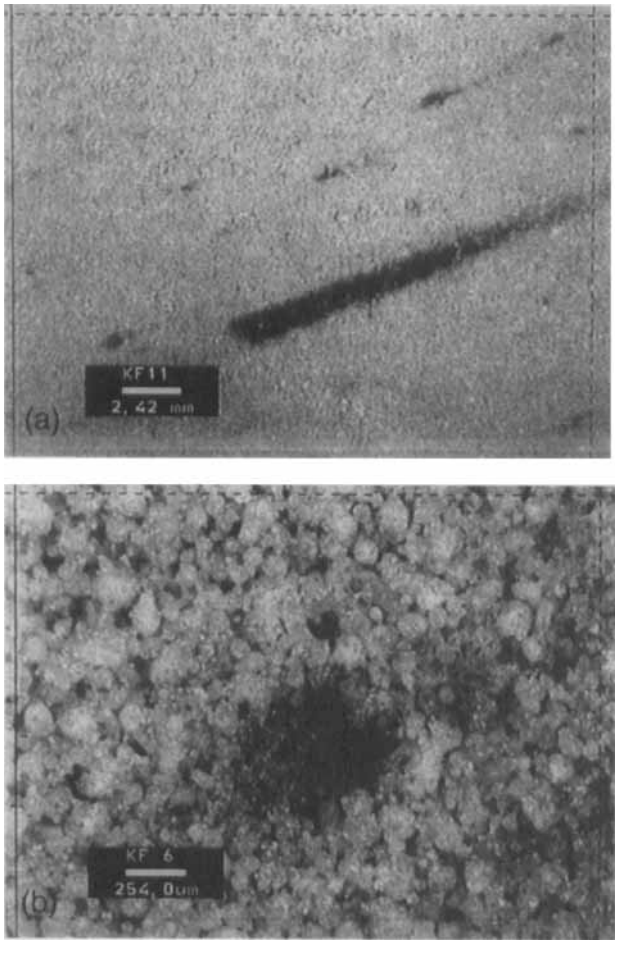
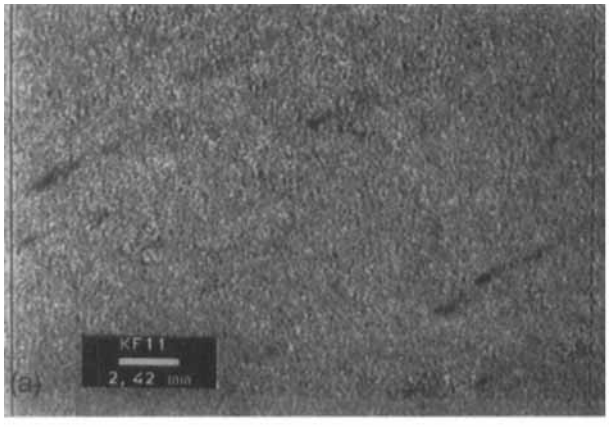


Figure 4. (a) and (b) Micrographs of blends of Lactose DC11 with 1% iron red pigment spread on paper: turbular mixer.

Figures 4(a) and 4(b) show micrographs of one of the preblends spread on white paper. Spots and stripes can be clearly seen. After screening the preblend through the Comil (for exact conditions, see run 3 in Table 7) and spreading on white paper, micrographs 5(a) and 5(b) were gained. As stripes and spots can still be seen, the Comil process, surprisingly, turned out not to be effective in the disagglomeration of iron oxide red pigment. The same was also observed in the other 3 experiments (Table 7). For this reason another experiment was done (run 5, Table 7) using the smallest round screen with the high impeller speed, but still red stripes were observed.

Red spots were no longer visible only when the material (run 3 and run 5 in Table 7) was passed through the Comil a second time, as depicted in Figs. 6(a) and 6(b) for run 3. This finding indicates that acceptable blends in some cases



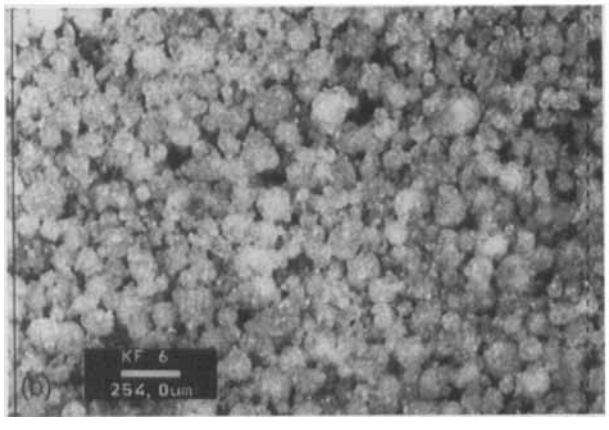
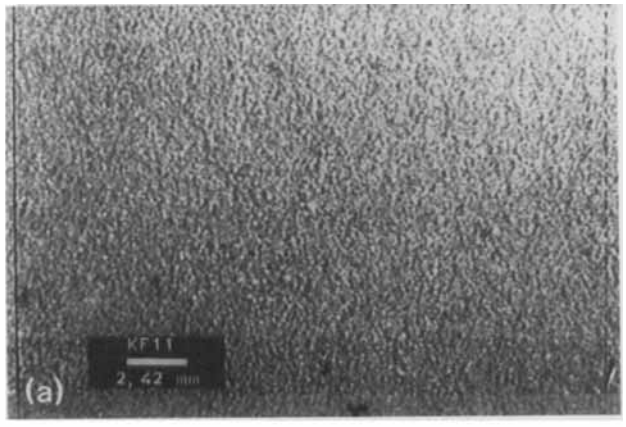


Figure 5. (a) and (b) Micrographs of blends of Lactose DC11 with 1% iron red pigment spread on paper: after first Comil passage.



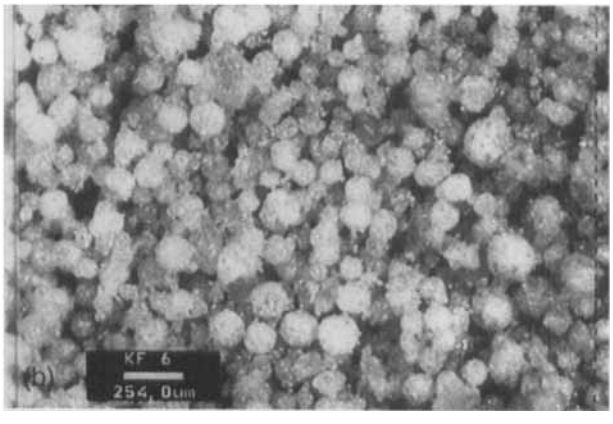


Figure 6. (a) and (b) Micrographs of blends of Lactose DC11 with 1% iron red pigment spread on paper: after second Comil passage.

may only be obtained when the materials are processed a second time.

CONCLUSIONS

The air jet sieving method was used to evaluate the effect of processing parameters and was found to be of good reproducibility.

Significant differences were found in particle size distributions when 3 batches of spray-dried lactose from a single supplier were investigated. It can be discussed whether these differences are of such significance to DC tableting that better specifications should be demanded from the manufacturers.

In contrast to model concepts regarding the shear action of conical screening mills, the Quadro Comil did not comminute particles during the screening step. It may even increase particle sizes, but this effect lies well within the range which was found for the variability of different batches of the same material. This finding was independent of all the different processing parameters and their combinations, and indicates that the Comil is suitable for processing the investigated DC materials at any of the processing conditions used.

Surprisingly, the disagglomeration effect caused by the shearing action of the impeller was found not to be sufficient when preparing mixtures with low proportion of a model drug even though the finest screens were used. Aggregates of a substance of high agglomeration tendency could only be destroyed when the blends were processed a second time. Nevertheless, even if processing twice through the Comil is necessary, this is thought to

be the procedure of choice because it involves fewer processing steps, needs less equipment, and is more gentle than wet granulation.

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