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Melt pelletisation of a hygroscopic drug in a high shear mixer
Part 1. Influence of process variables☆

R. Thies [a], P. Kleinebudde [b,*]

[a] *Department of Pharmaceutics and Biopharmaceutics, Christian-Albrecht-University, Gutenbergstraße 76, 24118 Kiel, Germany*
[b] *Institute of Pharmaceutics and Biopharmaceutics, Martin-Luther-University, Wolfgang-Langenbeck-Straße 4, 06120 Halle, Germany*

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Abstract

The applicability of a high shear mixer for melt pelletisation of binary mixtures of sodium valproate and glycerol monostearate was investigated. The effects of binder concentration, impeller speed, jacket temperature and massing time on mean pellet size and size distribution were examined in a 2^4-factorial design. Binder concentration and impeller speed were found to be the most important variables influencing the mean granule size and size distribution. An increase in each of those accelerated the granule growth. Due to the solubility of the drug in the molten binder very low amounts of binder were necessary for the formation of pellets. The modified high shear mixer was found to be suitable for batch sizes of 1–4 kg; granule growth was delayed with increasing load. A common pellet growth pattern, which can be divided into three phases, was derived and confirmed from all trials. The process was monitored by means of a torque measuring system. The torque–time curve can be used to detect the beginning of the destruction phase. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Melt pelletisation; High shear mixer; Glycerol monostearate; Hygroscopic drug; Granulation mechanism

1. Introduction

The use of a meltable binder seems to be suitable to produce pellets of water-sensitive materials, such as hygroscopic drugs and/or freely soluble drugs in the absence of water (Follonier et al., 1994). Thereby, water and organic solvents can be avoided during granulation/pellet production, which is desirable for both environmental and economic reasons. Melt pelletisation as a special type of melt granulation can be carried out by extrusion-spheronisation (Follonier et al., 1995), in a high shear mixer (Schæfer, 1996) or by other methods reviewed by Schæfer (1996). The

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* Corresponding author.
E-mail address: kleinebudde@pharmazie.uni-halle.de (P. Kleinebudde)

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equipment has to be heatable to temperatures above the binder's melting point, so that the binder can act as a liquid.

High shear mixing offers advantages as well as disadvantages compared to extrusion-spheronisation. High shear mixing was found to be a quick way to produce spherical, smooth pellets, which is important if the pellets are intended to be coated at a later stage. It is a one-step single-pot production process, needs less specialised equipment and high shear mixers for different batch sizes are common in the pharmaceutical industry. A disadvantage is the wider size distribution of those pellets compared to extruded ones (Kleinebudde and Nymo, 1995). Under certain conditions, granule growth by coalescence was reported to result in self-preserving size distributions (Knight, 1993). Kristensen and Schæfer (1995) found the predicted geometric standard deviation of about 1.31 to represent the minimum size dispersion achievable in a granulation process independent of the initial particle size. Furthermore, the process is sensitive to changes in the process and formulation variables (Schæfer et al., 1992a, 1993).

The aim of the present study was to show how pellets can be produced from binary mixtures of sodium valproate and a glycerol monostearate. In contrast to other melt pelletization studies, in this case the drug was highly soluble in the molten binder. Melt pelletization was performed in a modified high shear mixer, monitoring the torque to turn the impeller, the current, the product temperature and the jacket temperature. The robustness of the process was determined using a statistically designed experiment. Additional experiments were performed to add evidence to a postulated mechanism of granule growth.

2. Materials and methods

2.1. Material

Sodium valproate (SV, Katwijk, NL) was used as model drug. The apparent particle density is 1.14 g/cm^3 (Accupyc 1330, Micromeritics, USA). Sodium valproate is a hygroscopic and freely soluble substance which takes up water at a relative humidity of above 44% rh at 20°C. At higher humidity it liquefies quickly (Chang, 1979). The meltable binder was glycerol monostearate in fine powder form (GMS, Myvaplex 600P, Eastman, USA). Both substances were USP grade.

The solidification point of GMS (68°C) was determined by differential scanning calorimetry (DSC 7, Perkin Elmer, USA). Due to the solubility of sodium valproate in GMS (approx. 55 g SV/100 g GMS), the solidification point is lowered, depending on the amount of dissolved sodium valproate (Fig. 1). It was determined by DSC using mixtures of both substances.

2.2. Equipment

A vertical axis high shear mixer (P 10, Diosna, Germany) was used. The 10-l bowl (Fig. 2) was surrounded with a heating jacket, adjustable up to 120°C. In contrast to the commercially available mixer some modifications were made. The inner wall of the bowl and the three-blade impeller were lined with fluor ethylene propylene (FEP) in order to avoid adhesion of material during the mixing process. The range of the impeller speed was extended to 250–1060 rev./min. The chopper was removed during all experiments. The current of the motor and the torque to turn the impeller were measured during the process. The temperature of the product was recorded by a thermoresistance probe (PT 100), placed in the mixer wall at 6 cm from the bottom. A second probe was used to monitor the jacket temperature. The four

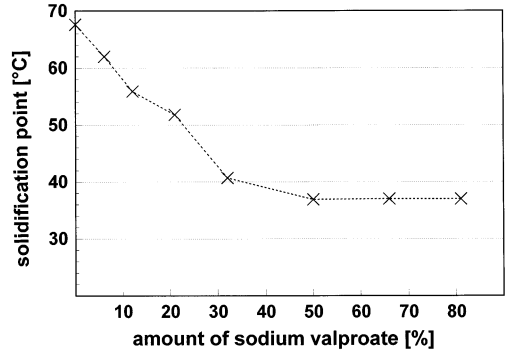

Fig. 1. Solidification point of binary mixtures of sodium valproate and GMS.

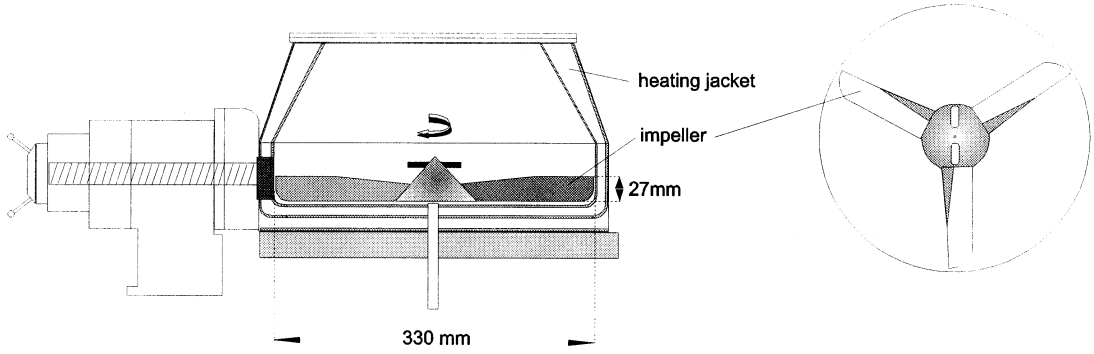

Fig. 2. Schematic drawing of the Diosna P 10 high shear mixer.

variables (current, torque, temperatures) were recorded every 50 ms and calculated every second as the mean of 20 values.

An experiment may be interrupted to take samples from the product bed. Alternatively, a cylinder with a diameter of 20 mm can be withdrawn through the mixer wall. Thus, samples can be taken without interrupting the process. Samples taken this way were found to be representative, despite the centrifugal force acting on pellets.

2.3. Pellet production

The mixer was thermostated for at least for 1.5 h at the temperature required prior to the experiment. The drug was first sieved (1000 μm) in a room below 40% relative humidity to destroy large agglomerates and then preheated in the mixer at low impeller speed (250 rev./min) for 10 min. Massing time started by adding the solid binder through an orifice in the lid and by adjusting the impeller speed according to the experimental plan. Binder concentration is expressed as percentage (% w/w) of the amount of drug. The relative humidity in the laboratory was below 35% rh, with temperatures between 25 and 30°C.

The prepared pellets were spread out at room temperature to cool down. A representative sample of about 100 g was taken for further characterisation by using a sample divider (type PT, Retsch KG, D-Haan). In some experiments the mixing process was interrupted to take samples at different sites of the product bed and restarted thereafter.

2.4. Pellet characterization

Pellet size, size distribution, the amount of lumps larger than 4 mm, and the amount of fines smaller than 500 μm were determined by sieve analysis, using a Vibro-type sieve tower (Retsch KG, D-Haan) with nine analytical sieves (500–4000 μm) for 5 min at medium vibration. The mean pellet size was described by the geometric weight mean diameter (d_{gw}) and the size distribution by the geometric standard deviation (s_g) (Schæfer and Wørts, 1977). Both parameters were calculated from pellets in the range of 0–4000 μm. Oversized pellets are included in the fraction of lumps.

2.5. Experimental design

During preliminary trials, standard conditions at which the mixing process resulted in pellets were determined. These served as the starting point for the following experiments characterised by an impeller speed of 525 rev./min, a binder concentration of 11.1%, a jacket temperature of 90°C and a mixing time of 20 min.

A full 2^4 factorial experiment ($n = 1$) including a centre point ($n = 3$) was carried out to estimate the robustness of the process. The parameters impeller speed, binder concentration and massing time were varied in the range of $\pm$ 10% and jacket temperature in the range of $\pm$ 5°C relative to the centre point experiment (Table 1). The results were evaluated using a model including the main effects and the two-factor interactions (Statistica

Table 1
Results of the 2^4 factorial experiment ($n = 1$) including a centre point ($n = 3$)

Amount of binder (%)	Impeller speed (rev./min)	Jacket temperature (°C)	Massing time (min)	Amount < 500 µm	Amount > 2000 µm	Amount > 4000 µm	d_{gw} (µm)	s_g	Additional work (W_a)	Group
10.1	475	85	18	34.6	2.0	1.9	312	3.04	6.1	1
			22	7.1	2.0	1.8	598	1.96	4.2	
		95	18	27.2	0.3	0.1	344	2.65	6.1	
			22	14.7	0.4	0.3	452	2.19	6.5	
	575	85	18	2.7	0.9	0.8	632	1.56	11.0	2
			22	1.9	1.4	1.3	716	1.53	5.0	
		95	18	2.1	1.0	0.8	726	1.51	9.8	
			22	1.7	1.0	0.8	1029	1.49	5.4	
12.1	475	85	18	1.6	3.6	3.2	798	1.63	7.5	
			22	2.1	3.4	2.9	918	1.64	7.7	
		95	18	2.4	2.6	2.2	975	1.64	11.1	
			22	2.5	3.6	2.7	1222	1.73	16.0	
	575	85	18	2.2	7.5	4.2	1351	1.72	11.9	3
			22	5.0	54.5	7.6	1555	2.41	34.8	
		95	18	6.9	63.5	12.3	1572	2.81	37.1	
			22	19.4	42.0	20.0	717	4.02	74.3	
				2.9	2.5	2.1	1006	1.68		
11.1	525	90	20	1.7	3.1	2.8	975	1.57		
				1.9	3	2.6	895	1.58		

5.1, StatSoft, USA). The factorial design was divided into two blocks, one including the runs at 85°C the other one the runs at 95°C jacket temperature. Each block was carried out over 1 day in a randomised order. Thus, the time for temperature equilibration between the different runs could be avoided.

To characterize the granule growth, a 43-min run with 12.1% GMS, an impeller speed of 475 rev./min and a jacket temperature of 85°C was carried out. Samples were taken after 9, 13, 17, 20, 22, 25, 28, 31, 34 and 37 min without interrupting the process.

A series of experiments was carried out to examine the influence of the mixer load on pellet quality ($n = 2$) under standard conditions. The load was varied between 1 and 4 kg and the time was adjusted to the course of each experiment to obtain pellets, without any further variations. The process was interrupted at several time points to take samples of 50–100 g, depending on batch size.

3. Results and discussion

3.1. Reproducibility

To determine the reproducibility of the process, the centre point of the factorial design was run in triplicate at different days. The values for d_{gw}, s_g, amount of fines and of lumps are shown in Table 1. The mean values of the X10, X50 and X90 quantiles were 736 ± 14, 970 ± 90 and 1304 ± 48 μm, respectively. This variation indicates that a product can be produced under these conditions with satisfying reproducibility. Subsequently, the following trials of the factorial experiment were done without replication ($n = 1$), since there were only small variations of the process conditions. Experiments with different batch sizes were not known to have the same reproducibility and consequently were carried out in duplicate.

3.2. Factorial design

The results of the 2^4-experiment are shown in Table 1 and the results of the statistical analysis in Table 2. The calculated mean size of 717 μm for the 22-min experiment at 575 rev./min, 95°C and 12.1% binder does not represent the true mean pellet size, which is obviously much higher. The value is biased because the lumps (20% > 4000 μm in this case) were not taken into account for the calculation of the geometric weight mean diameter d_{gw}. Therefore, this trial was excluded from the statistical analysis for d_{gw} and s_g. The correlation between the measured mean pellet size d_{gw} and that predicted according to the statistical model is shown in Fig. 3. The process was sensitive against changes of parameters in the chosen range regarding the pellet size and the size distribution. Analysis of variance showed that all four main factors were a significant influence on the mean granule size (Fig. 4a), but binder concentration and impeller speed were found to have the most important effect. These results are in good agreement with those of Schæfer et al. (1992b). There was only one significant influence for the geometric standard deviation s_g, the interaction between binder concentration and impeller speed (Fig. 4b). Impeller speed, binder concentration and their interaction were a significant influence on the fraction of fines and lumps. For the fines, two more interaction terms were found to be significant.

For further interpretation of the results, the 16 trials of the 2^4-design were divided into three groups, with the two most important variables binder concentration and impeller speed, both at low level, at different levels, and finally both at high level. The smallest pellets were produced in experiments with the binder concentration and impeller speed both at low level (group 1). A prolongation of massing time from 18 to 22 min resulted in an increase of the mean size d_{gw} and a decrease of the geometric standard deviation s_g. The amount of fines decreased markedly during this time from 27 to 15% and 35 to 7% respectively (Fig. 5a). In contrast to this, the amount of lumps remained below 2% in all cases (Fig. 5b).

In the eight experiments with one important variable at the high and the other one at the low level (group 2) the process resulted in pellets of an intermediate mean diameter (Fig. 4a) and a narrow size distribution (Fig. 4b). The amount of

Table 2
Results of the multiple linear regression analysis of the 2^4-factorial design[a]

	d_{gw} (μm)	*P*-value	s_g	*P*-value	Fines (%)	*P*-value	Lumps (%)	*P*-value	Additional work (J)	*P*-value
Mean	944.5	0.0000	2.05	0.0000	8.36	0.0007	3.92	0.0016	15.91	0.0013
(1) Impeller speed	242.2	0.0007	−0.01	0.9070	−3.14	0.0376	2.05	0.0231	7.75	0.0247
(2) Binder	343.4	0.0002	0.06	0.4800	−3.11	0.0386	2.96	0.0055	9.15	0.0133
(3) Time	105.8	0.0152	−0.02	0.8019	−1.58	0.2171	0.73	0.3008	3.32	0.2317
(4) Temperature	84.3	0.0316	0.11	0.2070	1.23	0.3224	0.95	0.1937	4.88	0.1018
1 × 2	67.6	0.0601	0.46	0.0038	6.26	0.0025	2.10	0.0214	6.71	0.0402
1 × 3	10.5	0.7065	0.16	0.1022	3.36	0.0299	0.70	0.3191	2.87	0.2922
1 × 4	38.5	0.2124	0.12	0.1849	1.06	0.3873	1.53	0.0606	3.12	0.2566
2 × 3	8.2	0.7688	0.18	0.0766	3.57	0.0241	0.68	0.3344	4.82	0.1054
2 × 4	48.0	0.1385	0.14	0.1307	1.30	0.2971	1.44	0.0724	4.69	0.1125
3 × 4	19.1	0.5034	0.03	0.7071	1.54	0.2269	0.32	0.6409	1.42	0.5858
Adjusted R^2		0.945		0.719		0.809		0.770		0.720

[a] For each response the coefficients and related *P*-values for the coded factors (main variables) and the two-factor interactions are shown. The adjusted R^2 for the overall model is given.

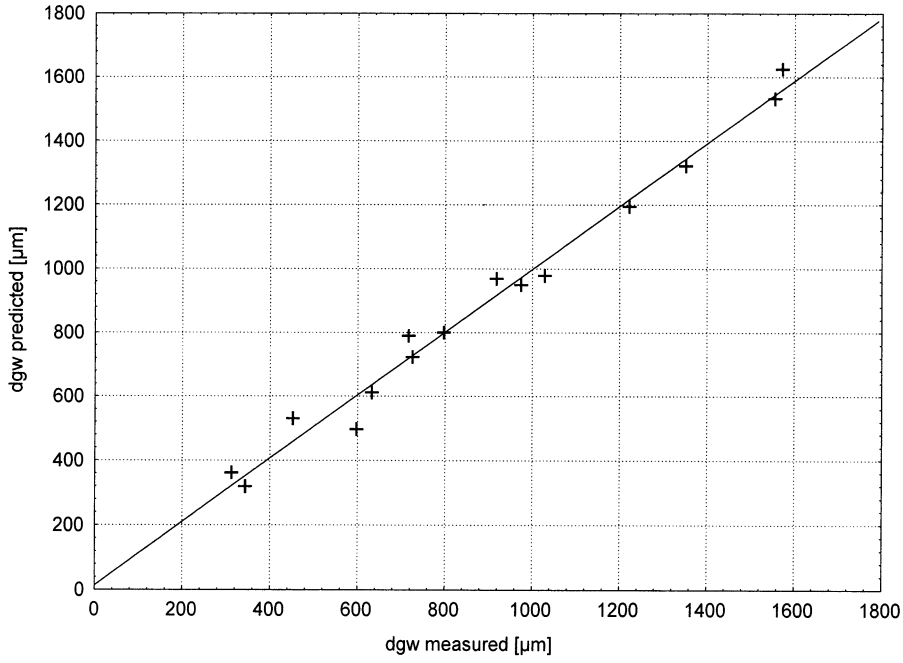

Fig. 3. Correlation between predicted and measured mean pellet sizes.

fines as well as the amount of lumps (Fig. 5c,d) were below 3.5% in all cases. The mean granule size was affected by jacket temperature and massing time: higher temperature and prolonged massing time resulted in larger pellets. There was, however, only little variation in s_g, which was in the range of 1.49 and 1.73 in all cases. This is reflected in the significant interaction term for impeller speed and binder concentration. If both variables are on a high level or on a low level, a high value for s_g is predicted, and a small value, if one variable is on a high and the other on a low level.

In the experiments with both impeller speed and binder concentration at the high level (group 3) the pellet size was found to be the largest (Fig. 4a). Nevertheless, differences were found when varying temperature and massing time. An increase in each led to faster granule growth compared to groups 1 and 2. Hence, the mean size at 95°C jacket temperature was higher compared to 85°C. The amount of fines and, simultaneously, the amount of lumps (Fig. 5a,b) increased with mixing time. Thus the size distributions became wider (Fig. 4b). This implies that, apart from further granule growth, a destruction of pellets occurred in these runs. The resulting pellets were found to be dusty, with a fine powder layer on the surface, whereas at shorter massing time and in all other runs of the design the surface was very smooth.

The results of the complete 2^4-design showed that an acceleration in granule growth was provoked by increasing binder concentration in all cases. This is assumed to be due to an increased deformability at collisions between agglomerates, because of a higher surface plasticity. Holm et al. (1985) found that a high deformability gives rise to a higher probability of coalescence of the agglomerates and thereby an increase of agglomeration growth. A higher impeller speed also augments the deformability at collisions and increases the densification of the agglomerates (Schæfer et al., 1992a).

In the presented factorial design the effect of a higher binder concentration was compensated by a lower impeller speed and vice versa. This was confirmed by the runs at the centre point of the

experimental design which yielded comparable results.

Compared to melt pelletization experiments described in the literature (e. g. Schæfer 1996) the use of about 10–12% of binder was rather low, whereas lactose or mannitol needed more than 20% of PEG to be pelletized in most studies. The low binder concentration might be due to the high solubility of the drug in the molten binder. Schæfer et al. (1990) were able to show that less binder liquid was necessary for wet pelletization experiments compared to melt pelletization in the case of a substance soluble in the aqueous binder liquid, but more aqueous binder was necessary in the case of insolubility. The authors argued that

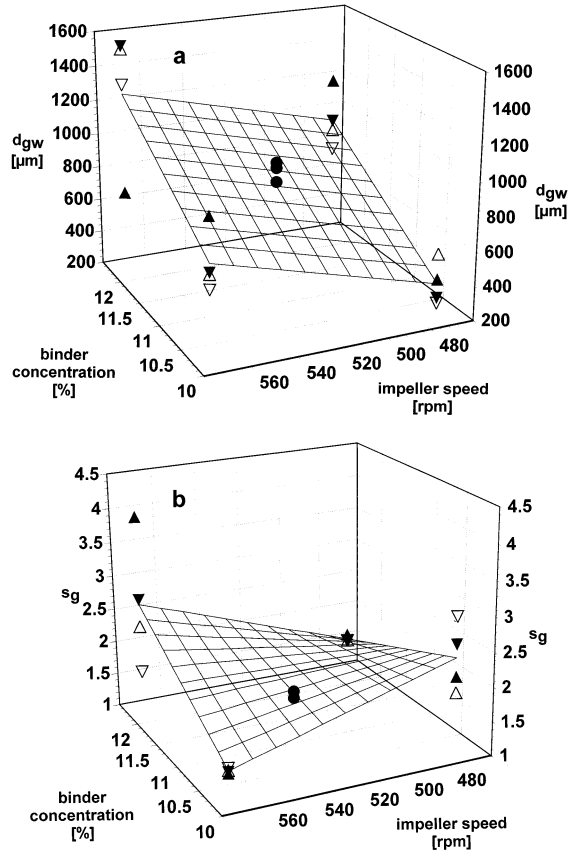

Fig. 4. Effect of binder concentration and impeller speed on mean pellet size (d_{gw}) (a), and the geometric standard deviation (s_g) (b) in melt pelletisation experiments. Massing time: 18 min (▼, ▽), 20 min (●), 22 min (▲, △). Jacket temperature: 85°C (△, ▽), 90°C (●), 95°C (▲, ▼).

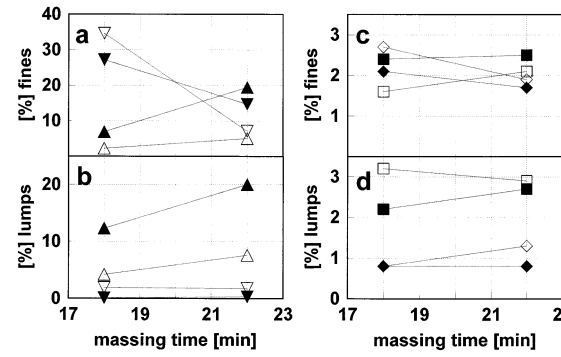

Fig. 5. Effects of massing time, impeller speed, binder concentration and jacket temperature on the amount of fines (< 500 µm) (a, c) and lumps (> 4000 µm) (b, d). Impeller speed: 475 rev./min (▽, ▼, □, ■), 575 rpm (△, ▲, ◇, ◆). Binder concentration: 10.1% (▽, ▼, ◇, ◆), 12.1% (□, ■, △, ▲). Jacket temperature: 85°C (open symbols), 95°C (closed symbols).

the dissolution on the surface of the particles reduced particle interactions and hence improved the deformability of the moist agglomerates.

It was concluded from the results of the three groups that all experiments followed the same pattern of granule growth during massing. This process can be divided into three phases. The first phase includes the formation of pellets and the start of pellet growth. In case of group 1, s_g decreased, but even after 22 min it was much higher than in group 2. The effect of decreasing s_g-values was provoked by the disappearance of fines, which were still in the range from 7 to 15% after 22 min. It may be assumed that further massing would continue this decrease in fines, yielding pellets of a narrower size distribution. It is well proven in the literature (Schæfer et al., 1992a,c) that the geometric standard deviation decreases with increased massing time. During the next phase, s_g was more or less constant for some time and the pellet size increased homogeneously. In this part of the process another granulation regime is assumed to take place. Size distributions of agglomerates are known to be self-preserving when the mechanism of growth does not change during the process (Kapur, 1978). Hence, all size distributions should have the same shape when using a logarithmic scale for abscissas. In the factorial design a self preserving distribution was

found only for the experiments of group 2, where there was almost no change in geometric standard deviation with prolonging massing time. This indicates a stable process and a homogeneous growth of the particles in the time range between 18 and 22 min. A third growth regime (group 3) is characterised by a simultaneous destruction of pellets and further granule growth, described as crushing and layering by Kapur (1978). Both, fine particles and lumps are generated, and the geometric standard deviation increases. The pellets are dusty, as the generated fines could not be embedded into the larger pellets. This destruction of pellets certainly occurs earlier in the process, too, when the pellets are not able to dissipate the kinetic energy and break down. The difference is that during earlier phases the fragments are able to form new pellets, while after a certain time this seems no longer possible and fines remain in existence. According to Tardos et al. (1997), critical granule sizes, depending on the shear force, are characteristic at the transition of one granulation regime to another.

3.3. Granule growth

To prove the assumption of the proposed granule growth pattern, an experiment was performed by the way of example with a binder content of 12.1%, 85°C jacket temperature and a rotation speed of 475 rev./min. The results are shown in Fig. 6. The total massing time was 43 min, which was long enough for all three phases of granule growth to occur. An increase in d_{gw} was observed with massing time. Again, the value at 43 min was biased due to the high amount of lumps (31.5% > 4 mm in this case). Calculating d_{gw} and s_g from granules in the range of 0–8000 μm leads to more reasonable values. They are depicted in Fig. 6 (open symbols). It is not appropriate to use the range of 0–8000 μm for the description of the pellet size distribution in all cases, however, because the lumps in the fraction > 4 mm may not necessarily be simply large pellets. This fraction may also contain fragments of a former bowl layer. Then, these lumps are not part of a pellet distribution and would bias the results towards too high values for d_{gw}.

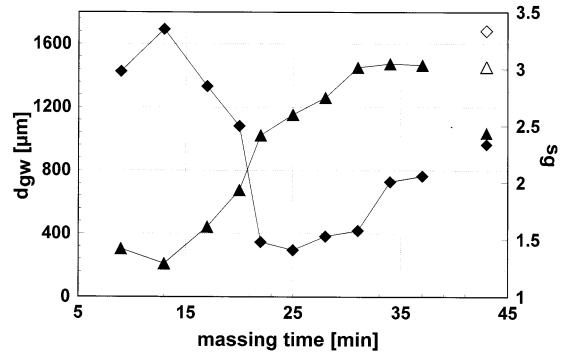

Fig. 6. Effect of massing time on mean pellet size (d_{gw}) (▲, △) and geometric standard deviation (s_g) (◆, ◇), calculated from pellets in the range of 0–4 mm (▲, ◆) and 0–8 mm (△, ◇). Impeller speed: 475 rev./min. Binder concentration: 12.1%. Jacket temperature: 85°C.

The geometric standard deviation was high at the beginning of the trial. Between 17 and 22 min, it decreased rapidly to low values. In this time range the process is assumed to shift from phase 1 to phase 2 due to a change in granulation regime. The amount of fines decreased (Fig. 7) from 60.1% after 9 min to 2.4% after 22 min, also indicating the end of the first regime. In the time period from 22 to 31 min, the amount of fines was low. With further massing it increased again, indicating the beginning of the destruction phase (phase 3). In addition to the increase in fines, the amount of lumps increased rapidly, resulting in wide size distributions.

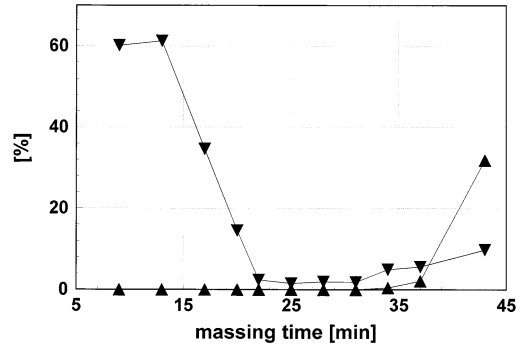

Fig. 7. Effect of massing time on the amount of fines (▼) and lumps (▲). Impeller speed: 475 rev./min. Binder concentration: 12.1%. Jacket temperature: 85°C.

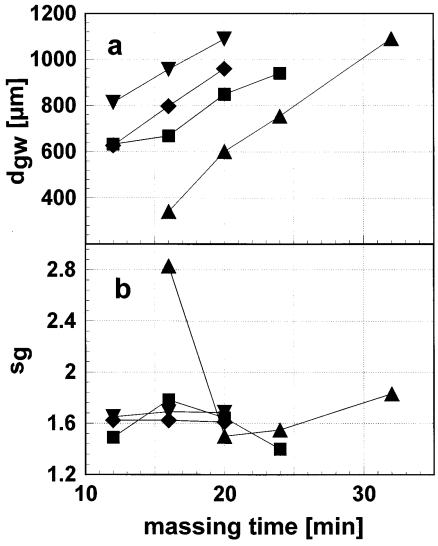

Fig. 8. Effect of massing time on mean pellet size (d_{gw}) (a) and on geometric standard deviation (b) with different mixer loads. Mixer load: 1 kg (▼), 2 kg (◆), 3 kg (■), 4 kg (▲). Impeller speed: 525 rev./min. Binder concentration: 11.1%. Jacket temperature: 90°C.

3.4. Influence of mixer load

The experiments were carried out in duplicate. The results shown are mean values of two experiments. The time necessary to produce pellets of a certain size increased with increasing mixer load (Fig. 8). The growth rate per min was nearly constant in the examined time range between 12 and 20 min in the case of 1–3 kg mixer load and from 16 to 32 min with the 4 kg load, respectively. At the same time there were only slight changes in geometric standard deviation s_g, which was low and in the range of 1.5–1.7. Only with a batch size of 4 kg a marked decrease in s_g was observed between 16 and 20 min massing time. According to the time course of a three-phase pelletisation process as described above, the change from phase one to phase two can be seen. After 20 min, a homogenous granule growth occurred, which is characteristic of the second phase. In the examined time range of the other experiments the mixing process has already entered that phase. All experiments were stopped before the destruction phase started.

The fact that pellet growth rate was nearly constant in the second phase of all trials, implies that the batch size had an effect on the duration of the first phase of the process. Otherwise the differences in mean pellet size during the second phase with different mixer loads could not be explained.

3.5. Process monitoring

In every production process the course of the process should be controlled by monitoring relevant product properties, such as product temperature or actual water content in the case of wet granulation. The rheological properties of the moist mass are of particular interest during granulation, because the agglomerate growth is assumed to depended on them. An important aim is the determination of the end-point, especially if the process turns into a destruction of the product. Many methods are established, reviewed by Kristensen and Schæfer (1987), such as measurement of the torque on the impeller shaft (Bier and Leuenberger, 1979) or the current of the impeller motor (Cliff, 1990), but they all measure the same principle. The torque T measured to turn the impeller was transformed into the mechanical power consumption P (Eq. (1)), the integral of the power over the time being the work W brought into the system (Eq. (2)).

$$P = 2\pi \cdot n \cdot T \tag{1}$$

where n = number of impeller rotations per s.

$$W = \int P \cdot \mathrm{d}t \tag{2}$$

Fig. 9 shows the power consumption–time diagrams of the factorial design experiment. The curves were found to be almost congruent when comparing the short and long trial. The deviation in Fig. 9aFig. 9b may be explained by the fact that particular lower curves present the first trial of a day, where the torque measurement equipment and motor oil was warming up.

When comparing all diagrams of Fig. 9, the more or less equal time course is obvious. Each course can be divided into two or three parts. A peak in the beginning is followed by a plateau

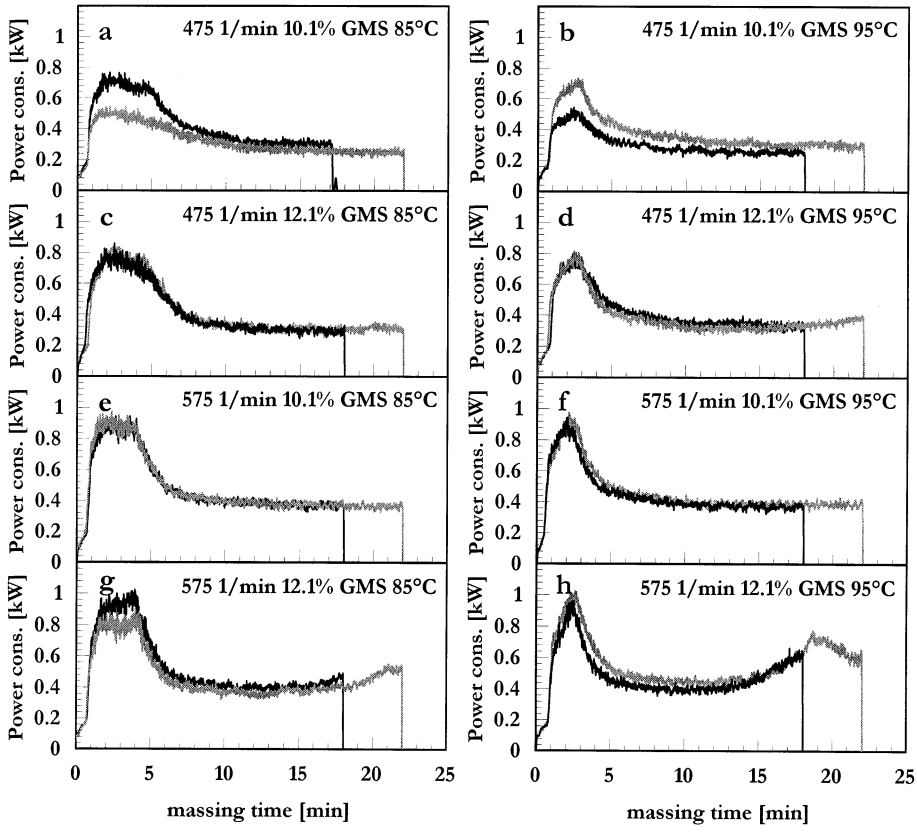

Fig. 9. Power consumption curves of the 2^4-factorial design.

and, in some cases, a second increase at the end of the experiment. The height of the first peak depends on the impeller speed (at 575 rev./min power up to 1 kW was brought into the product, at 475 rev./min the top power value was below 0.8 kW). The jacket temperature and the impeller speed affect the peak width, decreasing with increasing temperature and impeller speed. According to Schæfer et al. (1992b), the first peak reflects the melting of the binder. A similar rise is seen in aqueous agglomeration if the binder liquid is added at once (Horsthuis et al., 1993). The peak is assumed to be the essential phase of pellet formation. The second increase at the end of the trial is thought to mark the starting point of the destruction phase. The additional work W_a, brought into the product during the last 7 min of each trial is used to describe the size of this peak. This additional work is defined as the area between the power curve and a baseline value, defined to be the minimum value P_m of the sliding average power curve during the plateau phase (Eq. (3)). This correction is necessary because of differences in the height of the plateau phase, depending on the impeller speed (about 0.3 kW at 475 rev./min and 0.4 kW at 575 rev./min) and on the temperature of the torque measuring instrument.

$$W_a = \int_{t_e - 420}^{t_e} P \cdot dt - P_m \cdot 420 \quad (3)$$

where P is power consumption (W), P_m is the minimum power consumption of the plateau phase (W), W_a is additional work (J) and t_e is the massing time of the experiment (s).

Impeller speed, binder concentration and their interaction were of significant influence on the additional work (Table 2). During the second and third phase, the amount of fines reflects the extent

of destruction. It is possible to relate the amount of fines to the additional work (Fig. 10). Thus, the additional work can be used as a measure of the destruction phase. The runs of group 1 were not included in this graph, because they were in the first phase of the process.

4. Conclusions

It is possible to prepare 1–4 kg batches of pellets with a high load of a hygroscopic drug by melt pelletisation in a high shear mixer. In a factorial design it was shown that the process was more sensitive to binder concentration and impeller speed than to massing time and jacket temperature in the chosen range. The effect of a high binder concentration on mean granule size and size distribution could be compensated by a lower impeller speed and vice versa. It needs to be shown in future if this compensation holds true for a wider range of concentration and speed, respectively. The time to produce pellets of a certain mean size has to increase with batch size. The fact that the amount of binder was rather low was assumed to be due to the high solubility of the drug in the molten binder liquid. It was found that granule growth was principally accelerated by increasing jacket temperature and that pellet size increased with massing time, but these effects were dependent on impeller speed and binder concentration.

It is concluded that all experiments follow the same pattern, consisting of three phases: a pellet formation phase with a continuously decreasing amount of fines, followed by a phase of homogenous growth of pellets and ending in the destruction phase, the latter probably occurring in every experiment if the mixing time is long enough. The destruction phase is reflected by a second increase in the torque curve.

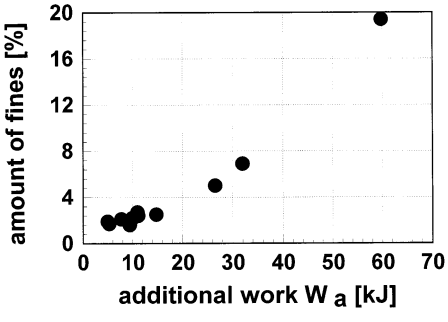

Fig. 10. Correlation between additional work W_a during the last 7 min of a trial and fines.

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