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PROLONGED RELEASE MATRIX PELLETS PREPARED BY MELT PELLETIZATION

I. PROCESS VARIABLES

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ABSTRACT

A melt pelletization process was investigated in an 8 litre laboratory scale high shear mixer using a formulation with paracetamol, glyceryl monostearate 40-50, and microcrystalline wax. The effects of jacket temperature, product temperature during massing, product load, massing time and impeller speed were investigated by means of factorially designed experiments. The maximum yield of pellets in the range of 500 - 1400μm was found to approx. 90%. For process conditions preventing deposition of moist mass, the process was found to be reproducible. Impeller speed and massing time were found to be important process variables. Remarkably low in vitro drug release rates were observed in USP-dissolution tests.

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INTRODUCTION

Melt pelletization is known as a process in which finely divided powder is agglomerated by means of a molten or softened binder and processed to spherical or almost spherical granules of almost the same size, preferably in the range 0.5 - 2.0mm. The product might be coated with an appropriate polymer in order to achieve prolonged release.

A melt pelletization process proceeds by agitation of a mixture of particulate solids and a meltable binder in a mixer, preferably a powerful high shear mixer [1]. As the binder is liquified by the heat developed by the agitation or by a heating jacket, it causes agglomeration similar to an aqueous binder solution [2].

Experience with melt pelletization using polyethyleneglycols (PEG's) has been reported recently [2]. PEG-based pellets used in prolonged release formulations have to be coated due to the PEG water solubility. If a hydrophobic binder could be used instead, it might be possible to obtain pellets possessing prolonged release properties directly and thus making coating superfluous. The prerequisite would be the application of a binder material melting below 120 °C, a pelletizing capability comparable to that of the PEG's and resistance to the enzymatic activity of the GI-tract. Release of drug from such a system would ideally be controlled by a diffusion process in the matrix formed by the meltable binder.

Nothing has been published so far on preparation of pellets in high shear mixers by means of hydrophobic meltable binders, but compression of granules prepared with lipophilic substances is described in numerous publications. Mixing of such meltable substances with solid particulate material at elevated temperature and subsequent milling of the cooled product may lead to granules possessing prolonged release properties directly [5,6,7]. As an alternative, the moist mass may be sieved prior to cooling in order to obtain granules [8].

The purpose of the present work has been to investigate the potentials of a melt pelletization process with lipophilic binders. The work is based upon the use of a laboratory scale high shear mixer which, due to an adequately high energy input to the agitated mass, has been found suitable for melt pelletization with PEG [3,4]. The present paper is concerned with the effects of process variables on melt pelletization of a mixture of calcium hydrogen phosphate, paracetamol, glyceryl monostearate 40-50, and microcrystalline wax. Preliminary studies have indicated that the formulation can be pelletized, and that prolonged release properties can be obtained. The following papers will deal with the effects of various binders, in vitro characterization of the drug release and mechanisms of release.

MATERIALS

Calcium hydrogen phosphate (Calipharm (dicalcium phosphate), Albright and Wilson Ltd.), paracetamol (Rhodapap, fine powder, Rhône-Poulenc) and glyceryl monostearate 40-50 (Glyceroli Monostearas 40-50 raspatus Grindsted A/S) were of Ph.Eur.grade while microcrystalline wax (Petrolite 195, Petrolite Corp.) was of NF XVII grade. The particle size distributions of calcium hydrogen phosphate and paracetamol were determined by a Malvern 2600 Lc laser diffraction particle sizer using a dry powder feeder (Malvern Instruments, UK). The mean particle sizes (by volume) were found to be 11μm and 19μm respectively. The melting ranges of the binders were estimated by a Perkin-Elmer DSC-7 (Perkin-Elmer Corp., CT, USA) using a scan rate of 10 °C/min. For the glyceryl monostearate 40-50 the melting range was found to be 55 - 60 °C, while 60 - 90 °C was the microcrystalline wax melting interval.

The composition of the formulation investigated was

paracetamol	12.5% m/m
calcium hydrogen phosphate	71.0% m/m
glyceryl monostearate 40-50	8.5% m/m
microcrystalline wax	8.0% m/m

Equipment

A Pellmix PL 1/8 (Niro-Fielder Ltd.) as previously described was used as pelletizing equipment [3,4]. It is supplied with the internal surface of the bowl lined with polytetrafluoroethylene, and a polytetrafluoroethylene cone mounted on the lid. Polytetrafluoroethylene is used in order to prevent adhesion of moist mass to the bowl [9]. A thermostat allows setting of a jacket temperature between 25 °C and 120 °C, but as mentioned in a previous report, the temperature of the jacket may rise during the process because it is heated by the product, which again is heated by the agitation [3]. The impeller blades were interchangeable, and in this study, curved impeller blades were used [4]. Jacket temperature, product temperature, impeller speed and power consumption were recorded. Before sieve analysis lumps and pellets larger than 2mm were collected on a sieve. Sieve analysis was made with a Fritsch Analysette (Fritsch, Germany) using a series of 9 ASTM standard sieves in the range of bottom tray - 2000μm. The samples were vibrated for 5 minutes at level "9"

The release properties of pellets from the 710 - 1000μm fractions were measured by a Hewlett Packard dissolution test equipment according to USP-guidelines. Basket rotational speed was 100rpm and Simulated Gastric Fluid USP (no enzymes) was used as medium. Paracetamol was determined spectrophotometrically at λ = 240 - 244nm.

METHODS

The starting materials were manually mixed and transferred to the mixing bowl, which was heated to a preset temperature by the jacket heating device. The jacket temperature levels investigated were 56 °C and 86 °C. All experiments were started at an impeller speed of 1200rpm. After approx. 5-8 minutes of mixing the product temperature reached 90 °C, whereafter the impeller speed was lowered to the value decided for the particular experiment. The massing times referred to below are the processing times after the product temperature had reached 90 °C. Product load levels refer to the weight of calcium hydrogen phosphate and paracetamol.

Effects of product temperature on the course of a melt pelletization process have been reported [1]. Preliminary experiments with the formulation investigated in the present study indicated likewise that the product temperature during massing may affect the product characteristics. In order to obtain a lower temperature level during massing, the lid of the mixer was removed after 5 minutes of massing, whereafter the massing was continued for 3, 5 ,7 or 9 minutes. Subsequently, the product was discharged onto a 26 x 28cm plastic tray and allowed to cool for 4 minutes before it was transferred to the mixer and run for one additional minute. Thus the total massing times were 9, 11, 13 or 15 minutes. In the experiments with high product temperature level the lid of the mixer was kept on throughout the entire process, and no interruptions of the massing were made.

The experiments were characterized by the geometric weight mean diameter ($\bar{d}_{gw}$ in μm) and the geometric standard deviation (s_{gw}). The content of aggregates larger than 2mm, the amount of deposits, and the yield of pellets in the range of 500 - 1400μm were calculated in percentage of the mass of the starting materials. Finally, the content of fines smaller than 180μm were determined in percentage of the sieve analysis sample weight.

In order to outline the experimental conditions suitable for detailed investigations a 2^4 - factorial designed screening experiment was carried out.

Subsequent experiments focused on the effects of

- Product temperature during massing and massing time
- Product load and impeller speed
- Impeller speed and massing time

The reproducibility of a melt pelletization process is described for formulations with PEG and lactose [2,3,4]. In addition 6 experiments with the present formulation run at identical conditions showed a mean particle size expressed as $\bar{d}_{gw}$ of 830μm and standard deviation of below 2%. s_{gw} appeared to be 1.44 with a standard deviation below 2%. These findings give reason to believe that a satisfying reproducibility can be found for products run at optimum conditions.

RESULTS AND DISCUSSION

Screening of process variables

A 2^4 - factorial designed screening experiment (n=1) was carried out with product temperature during massing (low or high), product load (800g or 1000g), jacket temperature (56 °C or 86 °C) and massing time (9 or 11 minutes) as independent variables. Impeller speed in the massing phase was 500rpm.

ANOVA of the data in Table 1 showed that low jacket temperature and high product load significantly increased the amount of deposits. This could be partly explained by the fact that low jacket temperature resulted in increased tendency of moist mass to solidify on the walls of the bowl. Pelletization of a formulation with lactose and PEG 3000 in the same mixer showed that jacket temperature optimum should be below the melting interval of the binder [3]. This indicates that optimum values for the process variables depend upon the melting behavior of the applied binder.

The amount of aggregates larger than 2mm was significantly higher at the low product load level. It is believed that for the low product load level the velocity in the upper parts of the moving mass was sufficient to tear off part of the deposits building upon the walls of the mixer, and result in larger particles and fragments in the product. This continuing breaking down and building up

TABLE 1

Screening experiment with product temperature during massing, product load, jacket temperature and massing time as independent variables. Impeller speed in the massing phase was 500rpm

Product temperature level during massing	Product load in g	Jacket temperature in °C	Massing time in minutes	$\bar{d}_{gw}$ in µm	S_{gw}	% < 180 µm	% >2mm	500-1400 µm fraction in %	Deposits in %
low	800	56	9	744	1.36	0.1	8.1	78.9	2.9
			11	725	1.37	0.1	5.8	79.8	3.4
		86	9	686	1.45	1.2	4.4	76.5	1.6
			11	726	1.40	0.2	4.3	81.0	1.6
	1000	56	9	769	1.40	0.7	4.2	81.0	5.1
			11	730	1.39	0.3	3.8	80.7	4.5
		86	9	719	1.54	1.4	2.3	79.9	2.5
			11	729	1.43	0.5	3.4	79.7	3.8
high	800	56	9	737	1.47	5.3	1.0	82.9	4.6
			11	765	1.41	0.5	1.1	86.6	3.1
		86	9	701	1.97	6.2	5.8	68.8	2.8
			11	826	1.65	1.8	4.8	77.7	1.5
	1000	56	9	729	1.59	2.2	0.9	79.0	6.9
			11	788	1.52	1.4	1.5	79.5	8.7
		86	9	644	2.05	8.1	2.0	69.4	2.8
			11	717	1.92	5.3	2.6	73.4	2.0

deposits is believed to have been less pronounced at the high product load level. In addition, the ANOVA showed significantly larger amounts of aggregates larger than 2mm for experiments with low product temperature during massing. However, a significant interaction was seen between product temperature and the jacket temperature. It could be observed that low product temperature and 56 °C jacket temperature lead to a higher amount of aggregates larger than 2mm, while high product temperature and 56 °C jacket temperature lead to smaller amounts of aggregates larger than 2mm. Product temperature did not affect the amount of aggregates larger than 2mm when the jacket temperature was 86 °C. It is assumed that the major portion of aggregates larger than 2mm had its origin in detached deposits. The amounts of aggregates larger than 2mm found in experiments with low product temperature were found to be relatively high, probably because the mass deposited at the junction between the cone and the wall were loosened during the dismounting of the lid after 5 minutes of massing in these experiments.

The particle size distributions of the products were significantly affected by product temperature during massing, jacket temperature, product load and massing time. It is assumed that the growth patterns for experiments with a tendency to build up deposits were inharmonic and affected by the random building up and breaking down of deposits. Consequently a relatively large s_{gw} was to be expected. Despite the deposits significantly small amounts of fines were found in products run at low jacket temperature, but due to interaction this effect was not significant at the low product temperature level. Inhomogeneous distribution of binder may partly explain these findings. If more binder was present in the moving mass than in the deposited mass, a larger growth potential in the moving mass would be expected. The consequence of this would be a more pronounced ability of the powder to suck up the fines in the moving mass. Another aspect is the particle size of the raw material. If the amount of powder deposited consisted of smaller and more cohesive particles than the powder in movement, a higher growth potential in

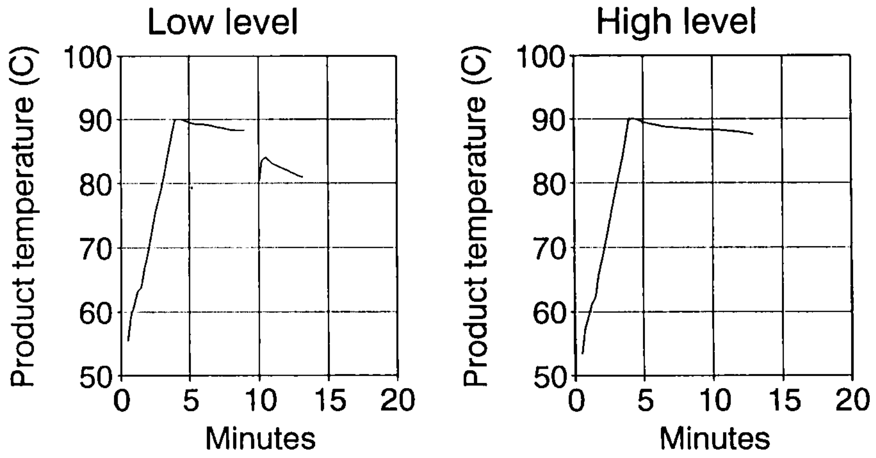

FIGURE 1 The product temperature progress during massing. Experiments run at low and high temperature level during massing. Product load: 800g, jacket temperature: 86°C, impeller speed 500rpm, total massing time: 9 minutes.

the moving mass would be expected. Finally the decrease in the amount of mass in movement would in itself tend to speed up the pellet formation and thereby eliminate the fines. Probably more than one of these possibilities are valid.

As a relatively high jacket temperature appeared to be advantageous, subsequent experiments were run with a jacket temperature of 86 °C.

Effect of product temperature during massing

A factorial experiment was carried out with 8 different experimental conditions (n=2). Product temperature during massing was varied at 2 levels as illustrated in Figure 1 for two experiments with a total massing time of 9 minutes.

The experimental conditions were identical for all experiments until 5 minutes after the product temperature had reached 90 °C. Subsequently, the low temperature level experiments were stopped for 1 minute and the lid was removed. During the following 3, 5, 7 or 9 minutes of massing the product temperature declined to 80 - 82 °C. Additional cooling to 70 - 72 °C was obtained in 4 minutes by the discharge onto the plastic tray before the products were massed for the last minute. In the experiments with high product temperature level the lid was on throughout the entire process and no interruptions of the massing were made. In these experiments product temperature declined from 90 - 91 °C to 86 - 88 °C during massing.

Massing time was varied on four levels (9, 11, 13 or 15 minutes). Product load was 800g, jacket temperature was 86 °C and the impeller speed was 500rpm. The obtained results are given in Table 2

In agreement with the preliminary screening experiment significant more deposition was seen in experiments performed with high product temperature. Further, it was found that a high product temperature resulted in larger $\bar{d}_{gw}$. It is assumed that the end point $\bar{d}_{gw}$ was higher, because the potential for growth by coalescence was generally higher, when the binder was a low viscous fluid as was the case, when the product temperature in the massing phase was high. Perhaps, at the low product temperature level the binder contracted and partly solidified during cooling and thereby lowered the potential for growth by coalescence.

This behavior of binder may also explain the significantly lower fines content and s_{gw} for low product temperature runs because a more and more viscous binder may lead to stronger interparticular binding forces between pellets and fines. In this situation growth by coalescence of larger agglomerates was assumed to be insignificant because the partly solidified binder counteracted the coalescence mechanism.

Photos of products massed at different product temperatures (Figure 2), showed that the surface of pellets run at low product temperature in the pelletization phase was smooth and homogeneous, and that these pellets were more spherical. Hence these pellets would be expected to posses the smallest surface available to dissolution fluid. In agreement with this assumption the observed release rates (Figure 3), appeared to be substantially different.

TABLE 2

Effect of product temperature during massing and massing time. Product load: 800g, jacket temperature 86 °C, impeller speed 500rpm.

Product temperature level during massing	Massing time in minutes	$\bar{d}_{gw}$ in μm	S_{gw}	% < 180 μm	% > 2 mm	500 μm -1400 μm fraction in %	Deposits in %
low	9	686 688	1.45 1.57	1.2 1.9	4.9 1.8	76.5 80.1	1.6 1.1
	11	726 734	1.40 1.49	0.2 1.1	4.3 3.7	81.0 82.2	1.6 1.9
	13	743 780	1.43 1.44	0.7 0.6	4.9 1.6	81.6 87.9	1.8 0.9
	15	832 784	1.37 1.42	0.2 0.5	5.0 1.9	85.9 88.0	1.5 1.1
high	9	701 716	1.97 1.86	6.2 4.5	5.8 4.3	68.8 72.1	2.8 2.2
	11	826 647	1.65 2.08	1.8 8.5	4.8 3.9	77.7 70.4	1.5 2.4
	13	831 862	1.69 1.66	2.3 1.0	2.7 3.2	79.3 78.4	2.8 1.7
	15	890 929	1.57 1.58	1.3 1.0	3.1 4.0	82.3 73.9	2.3 4.9

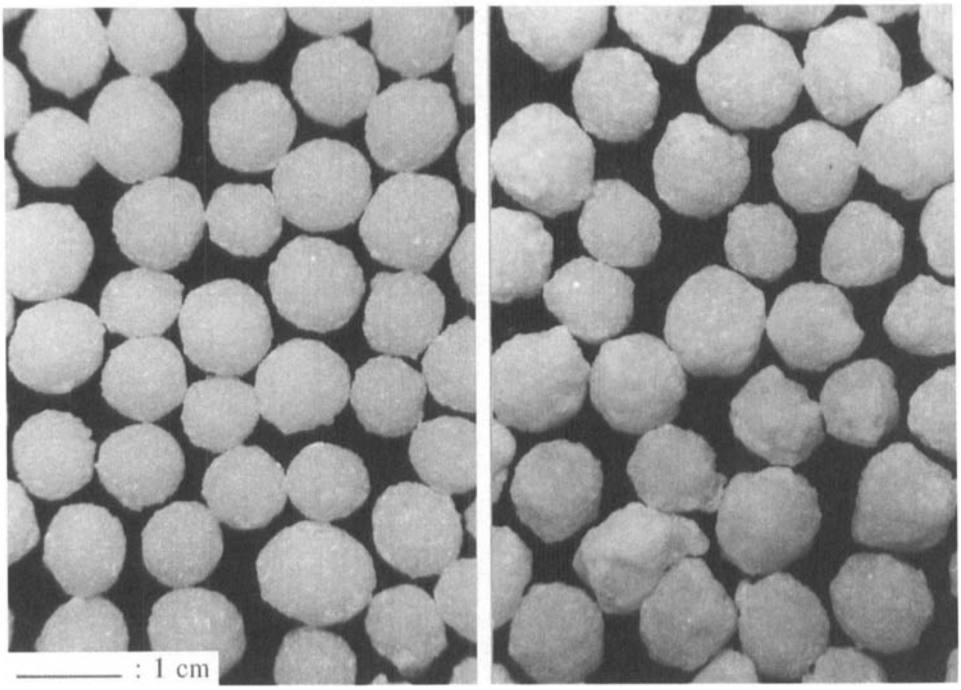

FIGURE 2 Effect of product temperature during massing. Photos of pellets from the 710-1000μm fractions of products run at low (left) and high (right) temperature level during massing. Product load: 800g, jacket temperature: 86°C, impeller speed 500rpm, total massing time: 9 minutes.

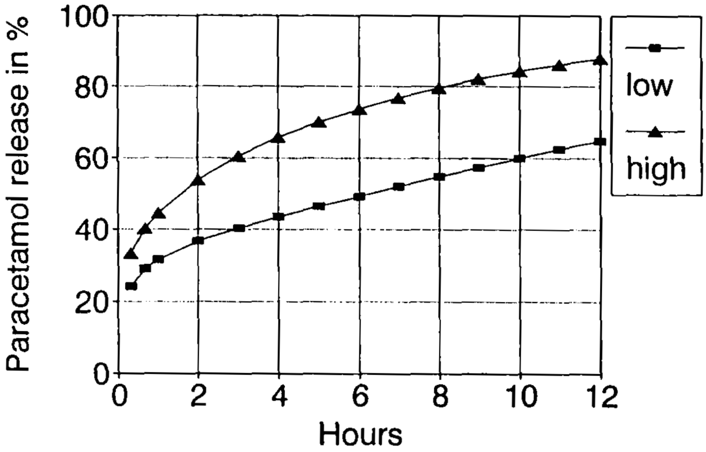

FIGURE 3 Effect of product temperature during massing on release. Key: Low: release of product run at low product temperature during massing and High: release of product run at high product temperature during massing. Product load: 800g, jacket temperature: 86°C, impeller speed 500rpm, total massing time: 9 minutes.

As reported in literature on wet granulation as well as on melt granulation, $\bar{d}_{gw}$ increased significantly with massing time while the s_{gw} decreased significantly [2,9,10]. Finally, the yield in the low product temperature experiments was significantly higher, just as the yield increased significantly with massing time.

As suggested by ANOVA of the data listed in Table 2, the photos reproduced in Figure 2 and the observed release rates (Figure 3), the subsequent experiments were run with low product temperature during massing.

The release rate and the dissolution type of kinetics of the release of drug from formulations such as the present will be the subject of publications under elaboration.

Effect of product load and impeller speed

The effects of product load and impeller speed were investigated by means of a factorial experiment with 9 different experimental conditions (n=2). Product load level was 600g, 800g or 1000g and impeller speed during massing was 400rpm, 500rpm or 600rpm. Jacket temperature was 86°C, massing time was 11 minutes and product temperature during massing was at the low level.

ANOVA of the data, which are presented in Table 3, showed significant and interacting effects of load and speed on the amount deposited. The dependence is illustrated in Figure 4. (r^2= 0,82)

During the experiments it was observed that the deposits at the lowest levels of speed and load occurred from the bottom and 3 - 5cm up along the bowl wall, while the deposits at the highest levels occurred at the upper parts

TABLE 3

Effect of product load and impeller speed. Jacket temperature: 86 °C , massing time: 11 minutes. Product temperature during massing was at the low level

Product load in g	Impeller speed in rpm	$\bar{d}_{gw}$ in μm	S_{gw}	% < 180μm	% > 2mm	500 - 1400μm fraction in %	Deposits in %
600	400	696 673	1.42 1.46	0.3 0.4	4.0 0.8	75.8 73.0	7.0 8.7
	500	840 985	1.37 1.46	0.1 0.2	16.4 2.1	74.4 80.2	1.8 3.7
	600	810 839	1.36 1.44	0.1 0.3	7.6 2.1	83.3 86.9	1.5 2.1
800	400	625 671	1.55 1.51	2.0 0.9	1.8 3.1	74.6 77.4	1.5 4.6
	500	726 734	1.40 1.49	0.2 1.1	4.3 3.7	81.0 82.2	1.6 1.9
	600	806 774	1.38 1.47	0.3 0.8	5.0 2.5	84.8 85.9	2.1 2.4
1000	400	650 632	1.67 1.70	3.3 3.3	0.7 0.3	77.9 76.9	1.4 2.1
	500	726 755	1.40 1.59	0.2 1.6	4.3 0.7	81.0 83.2	1.6 2.1
	600	772 906	1.62 1.49	2.1 0.5	6.7 5.7	72.3 72.3	6.9 12.0

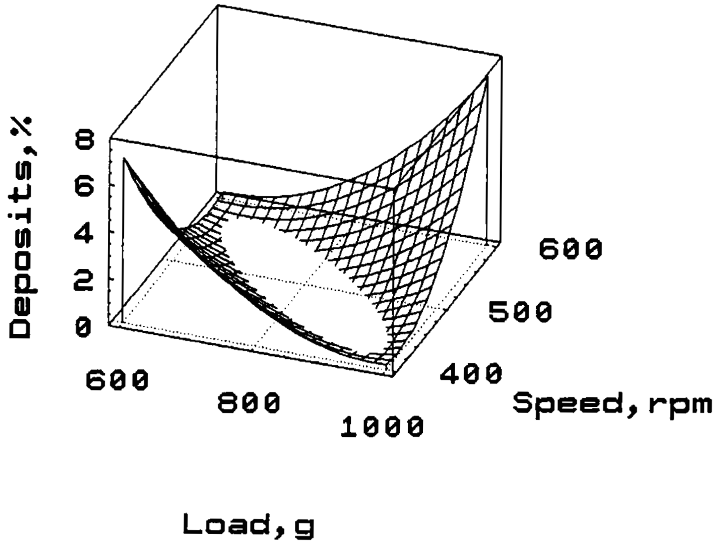

FIGURE 4 Response surface plot of the effects of product load and impeller speed on the percentage deposited ($r^2=0.82$). Jacket temperature: 86°C, massing time: 11 minutes. Product temperature during massing was at the low level.

of the wall. This demonstrates that a proper movement of the mass during pelletization is essential, if deposits are to be avoided. If load and speed were too low, the fluidization of the mass did not suffice to prevent depositing. On the other hand, if load and speed were very high, it was observed that the velocity in the upper parts of the mass was very low, and that powder tended to stall, thereby facilitating the deposition of the mass.

Finally, the junction between the cone and the wall of the jacket may have been starting points for deposits. As demonstrated by ANOVA and Figure 4 the smallest amount of deposits occurred, when the load was high or intermediate and the speed was low or intermediate. Similar low values of deposits were seen, when the load was low, and the speed high. It might be concluded that generally, a very high velocity gradient from the upper parts of the moving mass and downwards should be avoided.

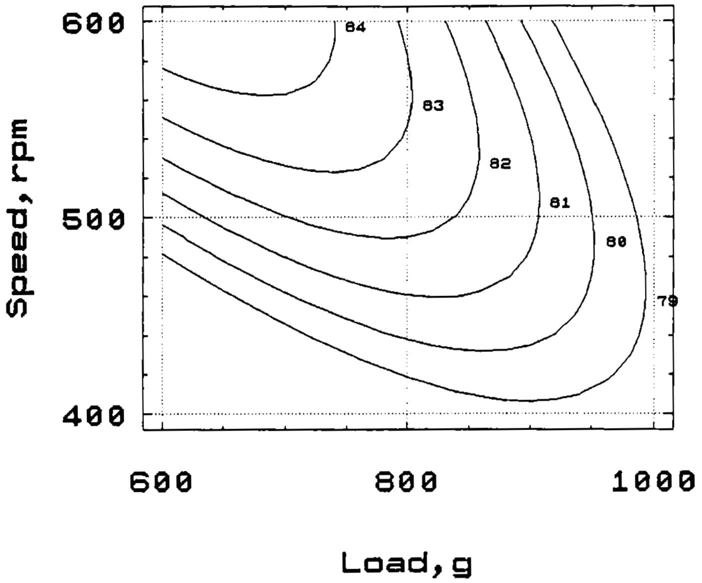

FIGURE 5 Contour plot of the effects of product load and impeller speed on the yield of the 500-1400μm fraction (%) (r^2=0.67). Jacket temperature: 86°C, massing time: 11 minutes. Product temperature during massing was at the low level.

$\bar{d}_{gw}$ was found to increase significantly with increasing speed and decreasing load. In addition, s_{gw} was found to decrease with increased speed and decreasing load. Finally, the amount of fines was found to correlate with s_{gw} (r^2 : 0,95). A simple interpretation of these findings can be based on an energy approach [4]. The higher amount of energy input experienced per mass unit, the higher growth potential, leading to relatively high $\bar{d}_{gw}$ and low s_{gw} because of a gradually decreasing amount of fines. Of course this approach is valid only, when the mass is moving in a harmonic and controlled way.

If in fact the mass moved in an appropriate way, high yield would be expected. Figure 5 shows a contour plot (r^2=0,67) of the yield obtained, and it is illustrated that high yields occurred at experimental conditions where mass did not tend to deposit.

TABLE 4

Effect of impeller speed during massing and massing time. Jacket temperature: 86 °C, product load 800g. Product temperature during massing was at the low level

Impeller speed in rpm	Massing time in minutes	$\bar{d}_{gw}$ in μm	S_{gw}	% < 180 μm	% > 2 mm	500 μm - 1400 μm fraction in %	Deposits in %
400	9	635 660	1.54 1.51	1.7 1.3	1.5 0.5	75.2 75.5	1.6 5.3
	11	625 665	1.55 1.46	2.0 1.2	1.8 0.2	74.6 80.9	1.5 2.2
	13	639 694	1.50 1.50	1.5 1.6	1.8 0.6	77.1 83.0	1.7 1.8
	15	658 709	1.48 1.39	1.4 0.5	1.6 0.4	80.0 85.6	1.7 2.8
500	9	686 688	1.45 1.57	1.2 1.9	4.4 1.8	76.5 80.1	1.6 1.1
	11	726 734	1.40 1.49	0.2 1.1	4.3 3.7	81.0 82.2	1.6 1.9
	13	774 780	1.41 1.44	0.4 0.6	3.6 1.6	82.4 87.9	0.8 0.9
	15	790 784	1.41 1.41	0.5 0.5	3.0 1.9	87.4 88.0	1.1 1.1
600	9	789 731	1.44 1.52	0.5 1.4	6.3 2.3	80.8 82.2	2.0 1.8
	11	806 765	1.38 1.45	0.3 0.9	5.0 2.7	84.8 85.6	2.1 1.8
	13	809 796	1.38 1.41	0.3 0.6	3.6 2.0	87.5 89.2	1.3 1.4
	15	841 835	1.35 1.35	0.2 0.3	2.9 1.5	90.0 92.2	1.4 1.1
700	9	789 764	1.44 1.50	0.7 1.3	2.8 1.2	85.6 86.8	1.4 1.2
	11	834 804	1.43 1.49	0.5 0.9	2.8 2.8	85.3 83.5	2.1 2.5
	13	852 852	1.47 1.46	0.7 0.6	4.2 5.8	82.2 80.1	3.5 4.6
	15	941 815	1.42 1.60	0.3 1.1	10.3 10.9	68.9 59.4	10.4 17.7

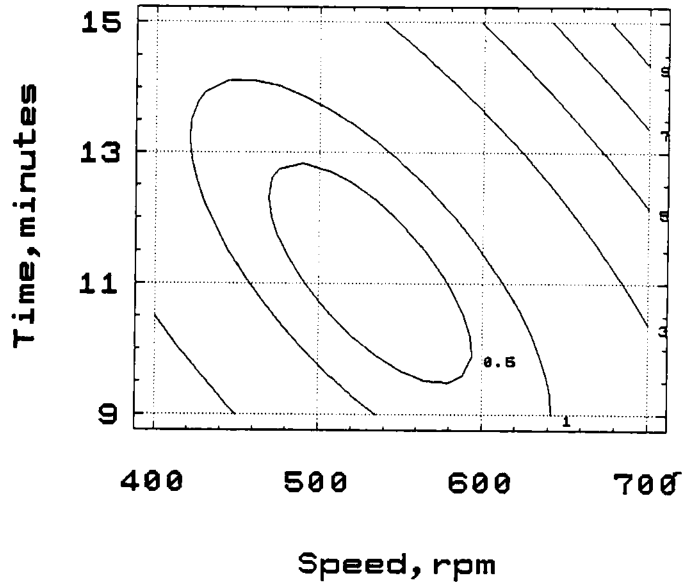

FIGURE 6 Contour plot of the effects of impeller speed and massing time on the percentage deposited (r^2=0.56). Product load: 800g, jacket temperature: 86°C. Product temperature during massing was at the low level. 0.5 - 9 : Percent mass deposited.

Effect of impeller speed and massing time

A factorial experiment was carried out with 16 different experimental conditions (n=2). Impeller speed during massing and massing time were varied at four levels (400, 500, 600 and 700rpm and 9, 11, 13 or 15 minutes). Jacket temperature was 86 °C, product load was 800g and product temperature during massing was at the low level.

ANOVA of the results reproduced in Table 4 showed that the amounts of deposits were significantly larger at 700rpm and massing time of 15 minutes. Furthermore, impeller speed and massing time showed a significant interacting effect on the amount deposited as illustrated in Figure 6 (r^2=0,56). The amounts of aggregates larger than 2mm were affected by impeller speed and massing time in a similar way. As earlier described, $\bar{d}_{gw}$ increased significantly with increasing impeller speed and massing time [3,4]. S_{gw} was found to be significantly larger at the lowest and highest impeller speed. For experiments run at very low impeller speed this was probably due to the significantly higher fines content caused by insufficient energy input and/or improper movement of the powder mass. When the impeller speed was very high, the reason was assumed to be an inharmonic growth pattern caused by depositing and milling of detached deposits.

S_{gw} decreased with massing time as found earlier [3,4]. The observed effects of massing time as gradually increasing mean pellet size and gradually narrowing size distribution is assumed to be a result of increasing densification and of liquid saturation as described in the literature, [2,3,4]. Intragranular porosity was not determined, although such data could have confirmed or weakened the assumption.

A significant maximum yield was found for the 600rpm impeller speed, while the effect of massing time suggested a maximum yield for 13 minutes of massing. Interaction of impeller speed with massing time showed a significantly lower yield for high levels of both factors.

CONCLUSIONS

The melt pelletization process showed good applicability of the formulation investigated, and the release characteristics of the products showed appreciably prolonged release when tested in vitro. The effect of jacket temperature, product temperature during massing, product load, impeller speed during massing, and massing time showed effect on the course of the pelletization. In order to avoid deposits and large amounts of oversize particles jacket temperature should be set at a high temperature near the upper part of binder melting interval. Furthermore, it appeared to be advantageous if the product temperature declined into the binder melting interval during massing. The optimum product load was approx. 800g of starting material (excl. 158g binder) and the optimum impeller speed was 500 - 600rpm. Massing time showed optimum effect at 11 - 13 minutes. The major part of the observed effects and their interactions are believed to relate to the amount of kinetic energy imparted to the mass. A high energy input will speed up the pelletization to a certain extent, whereafter the process becomes uncontrollable. The two key parameters controlling the energy input were impeller speed and massing time. Other formulations may show different optimum values for the parameters investigated in this paper.

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