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Notes

Parameters influencing granule quality using a continuous granulator

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Abstract

The parameters influencing granule quality using a continuous granulator were determined in an experimental design. The amount of granulation liquid, production capacity, temperature of the granulation liquid and rotational speed of the mixer were evaluated as quantitative parameters. The type of binder, its concentration and the design of the mixer were studied as the qualitative parameters. α-Lactose monohydrate was used as the model compound. The particle size distribution was only affected by the amount of granulation liquid. The friability of the granules was influenced by three parameters: the amount of granulation liquid, rotational speed of the mixer and type of binder and its concentration.

Key words: Continuous granulation; Experimental design

Wet granulation is used in the processing of solid dosage forms as tablets and pellets. Traditionally, granulation is performed batchwise but the advantages of a continuous production process (reduction of down time and labour costs, ease of automation and scale-up (Lindberg, 1988)) have led to increasing interest in continuous granulation. Continuous granulation can be performed with a continuous screw extruder (Goodhart et al., 1973; Lindberg, 1988), a continuous fluidized bed, a modified high-speed mixer (Ghali et al., 1991) and the Ivarson mixer (Lindberg, 1988). Nevertheless, very little attention has been paid to the influence of process parameters on granule quality using continuous granulation. In this study the influence of certain process and product parameters on the quality of granules made with a continuous granulator was assessed by means of an experimental design.

α-Lactose monohydrate 200 mesh (DMV, Veghel, The Netherlands) was used as a model compound. Polyvinyl pyrrolidone (PVP K-25) (BASF, Ludwigshaven, Germany) and drum dried waxy corn starch (DDWC) (Cerestar N.V., Vilvoorde, Belgium) were chosen as binders. Demineralised water was used as the granulation liquid in all

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experiments. Granules were prepared using a NICA Systems CMT-3 continuous granulator, currently distributed by NIRO-Fielder (Eastleigh, Hants, U.K.) (Appelgren, 1985; Lindberg, 1988). 15 s after starting the granulator 200 g of granules were collected, since a full-scale test can be carried out within a few seconds as both powder and liquid feed equilibrate immediately (Lindberg, 1988). The granules were oven dried for 2 h at 50°C and finally stored overnight at room temperature before physical testing was performed. The particle size distribution and friability of the granules were determined. The total amount of granules (expressed as a percentage) in the 250–1000 μm range was used for statistical analysis. After friability testing the amount of particles below 250 μm was determined and expressed as a percentage of the initial weight.

Table 1 lists the quantitative and qualitative parameters of which the influence on granule quality was evaluated by means of an experimental design and the experimental values of the different levels tested. The experimental values for the different parameters were chosen during preliminary tests. Table 2 shows the experimental design used in this study. All 24 experiments were performed in duplicate. In this study a production optimum was defined as the highest 250–1000 μm fraction yield with the lowest granule friability.

The results of the experiments with a parameter on the same level were pooled and the data were averaged taking into account that not all experiments were replicated the same number of times ('weighted' average). The average values are listed in Table 3. An analysis of variance (ANOVA) was performed on the average values in order to evaluate the influence of the different parameters on the response functions.

Particle size distribution: Only the amount of granulation liquid (G) had a significant influence ($p < 0.05$) on the particle size distribution. For a higher level of G, a greater 250–1000 μm fraction was obtained, but even the best result (G + 50.38%) indicated that a homogeneous particle size distribution was not achieved (Table 3A). At the highest level of G granulation was incomplete, since 14% of the granules were still smaller

Table 1
Quantitative and qualitative parameters and the experimental value of each level tested

Quantitative parameters			
G	+	12% (expressed as the moisture content of the wet granules leaving the granulator)
	−	9%
	0	6%
P	+	4000 g/min (the amount of granules leaving the
	−	2000 g/min
R	+	5000 rpm
	−	2500 rpm
T	+	40°C
	−	30°C
Qualitative parameters			
A	A_1	water (without a binder)
	A_2	a 6% aqueous dispersion of DDWC
	A_3	a 10% aqueous dispersion of DDWC
	A_4	a 5% aqueous dispersion of PVP
	A_5	a 10% aqueous dispersion of PVP
U	U_1	upper plate with 12 protuberances
	U_2	upper plate with 6 protuberances
B	B_1	bottom plate with 12 protuberances and a flat outer ring
	B_2	bottom plate with 3 protuberances
	B_3	bottom plate with 12 protuberances and a screwed outer ring

than 250 μm. Experiments on a planetary mixer and a high-shear mixer with the same model compound showed better results with less than 3% (Visavarungroj et al., 1990) and 1% (Visavarungroj and Remon, 1990) of the powder remaining below 250 μm, respectively. Theoretically better results should be obtained using a larger amount of granulation liquid. However, from a certain liquid/powder ratio lumps were formed and the process could not be kept under control. In this study the liquid pump operated at its highest capacity with P and G set at the highest level (producing 4000 g of granules per min containing 12% water). The limited capacity of the pump must also be considered. No other parameters had any effect on the particle size distribution using this model.

Friability: The amount of granulation liquid (G), rotational speed (R) and the type of binder and its concentration (A) had a significant effect ($p < 0.05$) on granule friability. An increase in

Table 2
Experimental design

Experiment number	Parameters evaluated						
	G	P	R	T	U	B	A
1	+	+	+	+	U_2	B_1	A_1
2	+	−	+	+	U_1	B_1	A_1
3	+	+	−	+	U_1	B_1	A_3
4	+	+	+	−	U_2	B_1	A_2
5	+	−	−	+	U_2	B_2	A_3
6	+	−	+	−	U_1	B_2	A_4
7	+	+	−	−	U_1	B_2	A_5
8	+	−	−	−	U_2	B_2	A_5
9	−	+	+	+	U_2	B_2	A_1
10	−	−	+	+	U_1	B_2	A_2
11	−	+	−	+	U_1	B_2	A_3
12	−	+	+	−	U_2	B_2	A_2
13	−	−	−	+	U_2	B_1	A_4
14	−	−	+	−	U_1	B_1	A_4
15	−	+	−	−	U_1	B_1	A_5
16	−	−	−	−	U_2	B_1	A_5
17	0	+	+	+	U_2	B_3	A_1
18	0	−	+	+	U_1	B_3	A_1
19	0	+	−	+	U_1	B_3	A_3
20	0	+	+	−	U_2	B_3	A_2
21	0	−	−	+	U_2	B_3	A_3
22	0	−	+	−	U_1	B_3	A_4
23	0	+	−	−	U_1	B_3	A_5
24	0	−	−	−	U_2	B_3	A_4

the amount of granulation liquid produced granules with a lower friability (Table 3B), possibly due to the fact that more lactose dissolved in the granulation liquid. The lactose in the aqueous phase recrystallized during the drying process, forming bridges between particles. When more lactose was dissolved, a greater number of bridges were formed and the friability decreased (Remon and Schwartz, 1987). The rotational speed of the mixer is the second important parameter influencing granule friability. The friability decreases with a decrease in the rotational speed (R) (Table 3B). This could be explained by the dwell time of the powder-liquid mixture in the mixer. At higher speeds the dwell time of the granules inside the mixer is extremely short, resulting in a decreased mixing time between the powder and the liquid. A short mixing time will reduce the possibilities of binding within the granule, resulting in a higher value for the second response criterion. The third parameter affecting the friability is the type of binder and its concentration (A). The highest friability was obtained when pure water was used as the granulation liquid (A_1

Table 3
'Weighted' average of the particle size distribution and friability data for the different values of the parameters investigated

Parameters	Number of levels				
	1	2	3	4	5
(A) Particle size distribution (in percentage)					
G	50.38 (+)	45.55 (0)	29.24 (−)		
P	41.69 (+)	42.01 (−)			
R	42.29 (+)	41.39 (−)			
T	40.91 (+)	42.85 (−)			
U	40.75 (U_1)	42.94 (U_2)			
B	42.63 (B_1)	37.00 (B_2)	45.55 (B_3)		
A	45.73 (A_1)	37.27 (A_2)	41.00 (A_3)	43.83 (A_4)	39.96 (A_5)
General mean: 41.9					
(B) Friability (in percentage)					
G	71.55 (+)	80.53 (0)	85.85 (−)		
P	76.46 (+)	81.90 (−)			
R	85.30 (+)	73.00 (−)			
T	80.06 (+)	78.70 (−)			
U	79.67 (U_1)	79.09 (U_2)			
B	81.37 (B_1)	75.71 (B_2)	80.53 (B_3)		
A	89.46 (A_1)	76.81 (A_2)	67.32 (A_3)	86.04 (A_4)	73.95 (A_5)
General mean: 79.4					

89.46%) (Table 3B). Adding a binder to the water conferred greater strength on the granules. Lower friability was observed for all experiments using a binder, except for A_4 (5% PVP) where no significant change in the friability compared to A_1 was noted. It appeared difficult to modify any of the parameters in such a way that the friability of the granulate was of acceptable quality. The experiments at the lowest friability (A_3 67.32%) showed a significant increase in quality compared to the highest friability value (A_1 89.46%). In comparison to the friability values obtained with a high-shear mixer (23.66%) (Visavarungroj and Remon, 1990) and a planetary mixer (25.17%) (Visavarungroj et al., 1990) using DDWC as a binder the friability values achieved in the continuous granulator are very high.

This study indicates that in order to increase the quality of a lactose granule the design of the continuous granulator tested could be improved. The manufacturers should certainly pay attention to the design of the mixer in order to allow a longer dwell time of the granules inside the mixer, resulting in greater energy transfer into the powder/liquid mixture.

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