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Control of fluidized bed granulation

I. Effects of spray angle, nozzle height and starting materials on granule size and size distribution

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The instrumentation of a fluidized bed granulator (Glatt, WSG 15) is described and the registration of inlet air temperature, product temperature and exit air humidity are discussed.

Granulations were prepared at different spray angles and nozzle heights. At extremely low values of spray angle the granule size decreased, whereas no appreciable influence was found at higher values. The spray angle showed no significant effect on size distribution. Increasing nozzle height resulted in a narrower granule size distribution, but had no significant influence on granule size.

The influence of the starting materials was examined using varying mixtures (4:1, 1:1 and 1:4) of lactose and starch (maize and potato). Increasing starch content and decreasing particle size resulted in decreasing size of the final granules.

Control of product and process variables is a prior requirement to the production of granulations with reproducible technical and biopharmaceutical properties. Granulation in a fluidized bed carried out under a combination of accurately monitored experimental conditions is a suitable method of controlling the granulation process.

Agglomeration is caused by complex interactions of several variables (Table 1), and a knowledge of the effect of each is therefore necessary for controlling the granulation process. Several authors (1, 3-5, 7, 9, 10, 12-19) have studied some of the variables, but no complete evaluation has as yet been carried out.

In the present and later papers the results of a study carried out in order to establish which variables are of importance in the control of granule size and size distribution will be presented. This paper deals with the influence of spray angle, nozzle height and starting materials.

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Table 1. Variables in fluidized bed granulation.

Product variables	*Process variables*
Starting materials and their particle size	Apparatus
Binder	Bed load
Binder concentration	Atomization of binder solution
Quantity of binder solution	Nozzle height
Binder solution temperature	Spray angle
	Liquid flow rate
	Fluidizing air velocity
	Inlet temperature of fluidizing air
	Processing time

Some authors (3, 17) have found that decreasing nozzle height results in increased granule size, whereas others (9, 10, 19) found no effect of this factor. However, nozzle height seems to influence the granule size distribution (15). Since *Thurn* (19) varied spray angle and nozzle height simultaneously, the influence of spray angle on granule size could not be determined. Other results of the effect of spray angle on granule size have not previously been reported. Nozzle height and spray angle are not expected to be main variables, and therefore a selected combination of these factors was maintained in the subsequent experiments.

Although various starting materials were applied to the fluidized bed granulations described in literature, direct comparison of the results is impossible due to the different experimental conditions. No systematic investigations concerning the influence of the starting materials and their particle sizes on the size of the final granules have been published hitherto although they can be expected profoundly to affect granule properties. The influence of ratio of mixing and particle size of starch and lactose on granule size and size distribution was examined. Based on these results an appropriate mixture of starting materials was selected for the remaining investigations.

The experiments were carried out in a single apparatus, so the influence of its construction and size was not examined.

Investigations on the effect of air velocity are complicated by the fact that the minimum fluidization velocity depends on particle size (2) and on particle humidity (6), and as both change gradually during the granulation process it is not possible to keep this factor constant. With the object of obtaining an approximately uniform motion of particles *Ormós et al.* (13) kept the bed expansion constant by continuously varying the air velocity. Increased bed expansion resulted in decreased granule size (15). In practice only small variations in bed expansion are possible since an increase leads to additional clogging of the exhaust air filter, while a

decrease may result in incomplete fluidization. Instead, bed expansion was kept constant by varying the air velocity.

The effects of the remaining variables on granule size and size distribution will be reported later.

Experimental

Materials and formulation

Starting materials were 15 kg of various mixtures (4:1, 1:1, 1:4) of lactose (two particle sizes) and starch (maize and potato). Particle size distributions estimated by counting at least 1,000 particles microscopically are shown in Fig. 1.

3,500 g of a 4 % aqueous gelaine solution, prepared by dissolving the gelatine powder in water at about 50° C and then keeping the mixture at 40° C in a thermostat for about 1 h, was used as binder solution.

Equipment

A fluidized bed spray granulator (Glatt, model WSG 15) equipped with a pneumatic nozzle (Schlick model 941-943/7) with a liquid orifice of 1.8 mm in diameter was used.

General procedure

The starting materials were passed through a sieve with a screen opening of 0.23 mm and placed in the product container. Mixing took place until the inlet air had reached the desired temperature, which took about 15 minutes after which the spraying of binder solution commenced. The shaking device was activated every second minute during the granulation phase and frequently during mixing and drying.

The fluidizing air velocity was regulated by inlet and exit dampers to keep a constant relative bed expansion of the order of magnitude of 1.6 (15) corresponding to an air velocity of about 1 m/sec during mixing and the last part of the drying phase. The maximum air velocity during the granulation phase varied between 1 and 3 m/sec depending on granule size and wetting of the granulation surface.

The air pressure at the nozzle was maintained at 4 ato and the volume of air was regulated by a flowmeter. Unless otherwise stated the nozzle height was set in position 7, corresponding to a height of 36 cm above the upper edge of the product container, and the air dome on the nozzle head was set in the number 5 position.

The drying was controlled by measuring the difference in temperature between the product and the wet bulb and terminated at a product temperature of about 5° C above the wet bulb temperature of the drying air. This difference is related directly to the moisture content of a given material as described by *Harbert* (8).

Instrumentation

Inlet temperature of the fluidizing air, product temperature and humidity of the outlet air were recorded (Philips model PM 8235) during the process via two temperature sensing probes (Wallace Ni-68/1000) and a lithium chloride cell (Ersec LC-62/1000).

A hot wire anemometer (Lambrecht No. 641bN) was used for measuring the air velocity under the air distributor. Atomizing air flow rate was measured by a series

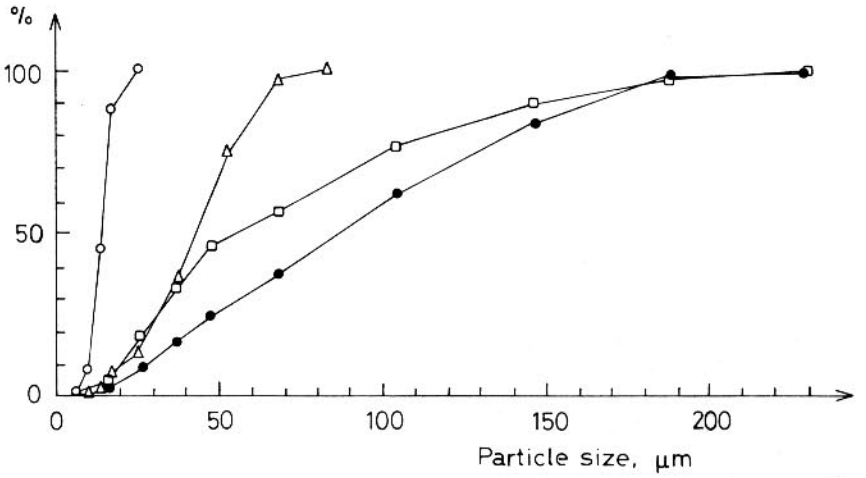

Figure 1. Cumulative particle size distributions (by weight) of the starting materials.
○: maize starch △: potato starch
●: lactose, crystalline □: lactose, fine-crystalline

of four flowmeters (Fischer & Porter model D10A1197A) covering the range of 0-70 Nm^3/h at 4 ato.

Liquid flow rate was controlled by the scale of the dosage pump and was further checked by monitoring the spraying time. The relative standard deviation was found to be about 2 %.

Granule size and size distribution

Granule size distribution was determined by sieve analysis with a rotating sieve shaker (Retsch model 330, position 70). The sieves used were divided into two series which include screen openings of 74, 125, 177, 210, 250, 297, 352, and 352, 420, 500, 590, 707, 840, 1000, 1410 and 2000 µm, respectively. Approximately 100 g of granulation were used for each analysis, and the sieves were shaken for 15 minutes under regular tapping. Sieve analyses were performed in triplicate for each batch of granulation, and the results reported are the average values.

In agreement with the results of other authors (9, 11, 17) it was shown that granule size distribution could be described by the log-normal distribution. Therefore the geometric-weight mean diameter (d_{gw}) and the geometric standard deviation (s_g) were used for characterizing granule size and size distribution. On the basis of results from the sieve analyses the values of d_{gw} and s_g were calculated from eqs. (1)-(2):

$$d_{gw} = \text{antilog} \frac{\Sigma w_i \cdot \log d_i}{\Sigma w_i} \quad (1)$$

$$(\log s_g)^2 = \frac{1}{\Sigma w_i} \cdot (\Sigma w_i (\log d_i)^2 - \frac{(\Sigma w_i \cdot \log d_i)^2}{\Sigma w_i}) \quad (2)$$

where d_i is the mean diameter and w_i the weight of sieve fraction number i. From 10 estimations of d_{gw} the relative standard deviation of the sieve analysis was found to be about 2 %.

Results and discussion

Registration

A record of inlet air temperature and of product temperature and outlet air humidity as a function of the processing time is shown in Fig. 2. Mixing and heating were started at the time 0 min. When the inlet air temperature is raised, that of the material increases. The rise in air temperature results in evaporation of moisture from the starting materials, and the humidity of the outlet air is therefore simultaneously increased.

After about 15 min the spraying of binder solution was started, and the outlet humidity quickly increased to a maximum after which it dropped slightly and was constant during the rest of the spraying time. The maximum is due to lower air velocity caused by a clogging of the exhaust air filter, which is most intense at the start of the granulation phase.

The granules were cooled by evaporation of moisture from the surface, and when this was saturated by the binder solution the product temperature remained at the wet bulb temperature, which depends on the temperature and humidity of the drying air.

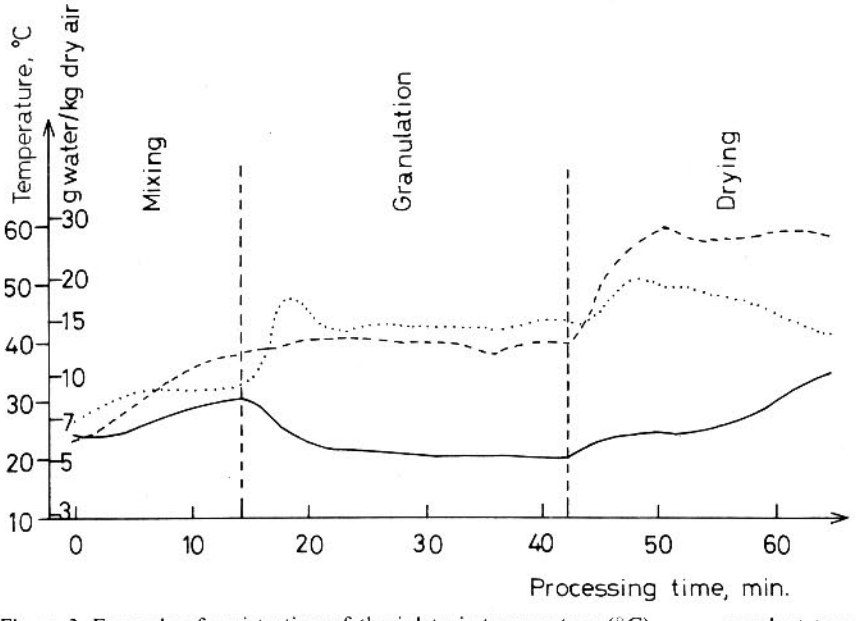

Figure 2. Example of registration of the inlet air temperature (°C) ----, product temperature (°C) —— and exit air humidity (g water/kg dry air) ..... during a fluidized bed granulation process.
Desired inlet air temperature: granulation phase 40°C; drying phase 60°C.

After granulation the temperature of the inlet air was raised to increase the rate of drying. This resulted in an increased humidity of outlet air, and the product temperature rose to the wet bulb temperature corresponding to the air temperature in the drying phase.

After drying for about 10 min the surface of the granules was no longer saturated, and the product temperature rose to about the wet bulb temperature due to a diminished drying rate and thus a decreased outlet air humidity.

Spray angle and nozzle height

The combination of spray angle and nozzle height determines the wetted area of the bed surface (Fig. 3). The spray angle is regulated by the setting of the air dome on the nozzle head.

Three levels of both nozzle height and spray angle were examined. The combination of the largest values of the two factors resulted in complete wetting of the cross-sectional area of the material container. The results of the experiments are given in Table 2. The values of spray angle are only approximate as a sharp distinction of the spray cone was impossible.

The effect of nozzle height on granule size was found by a two-factor analysis of variance not to be significant, the effect of spray angle, however, was significant at the 1 %-level. It was shown by the analysis that the effects of air dome settings 5 and 1.2 could not be separated, whereas air dome setting 2 resulted in a smaller granule size. A possible explanation of the effect of spray angle could be that it influences the drop size of the atomized binder solution.

The effect of nozzle height on the standard deviation was found to be significant at the 5 %-level. Increasing nozzle height resulted in de-

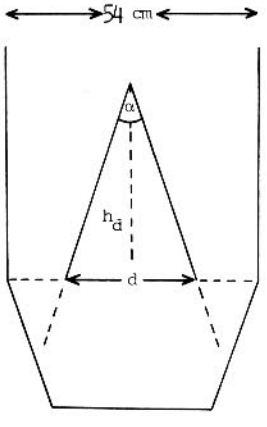

Figure 3. The influence of the position of the nozzle on the diameter, d, of the wetted bed surface area. α is the spray angle and h_d the nozzle height.

Table 2. The granule size (d_{gw}, μm) as a function of nozzle height and air dome setting.

Starting materials: 80 % fine-crystalline lactose + 20 % maize starch. Liquid flow rate: 150 g/min. Nozzle air flow rate: 10 Nm^3/h. Inlet air temperature: granulation phase 40°C; drying phase 60°C.

Nozzle height h_d (cm)	Air dome setting		
	2 (ca. 30°)[1]	5 (ca. 40°)	1.2 (ca. 60°)
21	153 (2.35)[2]	191 (2.22)	201 (2.22)
36	177 (2.24)	214 (1.97)	202 (2.18)
51	164 (1.96)	194 (1.91)	202 (1.90)

1. The values given in parantheses are spray angles (α).
2. The values given in parantheses are geometric standard deviations (Sg).

creasing standard deviation in accordance with the results of *Ormós et al.* (15), and this observation can be explained by the more uniform wetting obtained by the simultaneous increase in wetted bed surface area.

Increasing spray angle should have the same effect on s_g, but no significance was found by analysis of variance. A possible explanation is that the effect of an alteration of the wetted surface area in this case is counteracted by a simultaneous change in drop size.

Starting materials

Blends of lactose and starch were selected as starting materials, because they are generally used as excipients in tablet formulations and because of their different water-binding properties. When binder solution is added, this is mainly present as free water on the surface of the lactose powder, whereas starch extensively binds the water by absorption.

The influence of varying particle sizes on the final granule size was studied by using two different particle sizes of lactose and two types of starch (maize and potato) (Fig. 1). A small variation in nozzle air flow rate usually gives an appreciable change in granule size (3, 16, 18, 19), and therefore nozzle air flow rate was varied to select the blend of starting materials which is most sensitive to variations in experimental conditions.

The results are given in Table 3. The influence of the factors was estimated by analysis of variance using a factorial design. Since mixing ratio occurs at three levels, the analysis consists of three 2^4-factorial designs with varying levels of mixing ratio.

The effect of nozzle air flow, mixing ratio and type of starch (maize or potato) on granule size was found to be significant at the 0.1 %-level. In one of the factorial designs the effect of particle size of the lactose was significant at the 5 %-level.

Interactions were found between air flow and mixing ratio and between mixing ratio and starch. They were reflected by an increase in influence of nozzle air flow as lactose content rose and, in the case of maize starch, by an increase in influence of mixing ratio. Consequently, the blends containing 80 % of lactose seem to be those most sensitive to variations in experimental conditions and they were used in the subsequent experiments.

Increasing nozzle air flow resulted in decreasing granule size in accordance with previous observations (3, 16, 18, 19).

The standard deviation seems to increase as granule size decreases, but it is difficult to decide whether the change in standard deviation is caused by the simultaneous change in mixing ratio.

In order to explain the influence of mixing ratio and particle size on granule size the surface areas of the different mixtures were approximated (Table 4).

Comparison of Tables 3 and 4 shows that increasing surface area results in decreasing granule size. However, differences in surface areas are not the only effect of starting materials. A given change in surface area caused by variation of mixing ratio had a greater influence than the same change obtained through variation of particle size.

Granulation is initiated by formation of liquid bridges between primary particles. The number of bridges depends on the quantity of free water present on the surface of the starting materials. Increasing surface area and absorption of water result in incomplete wetting of the surface if the quantity of binder solution is unchanged, and, thus, decreasing particle size and increasing starch content result in decreasing granule size.

The slight influence of the lactose particle size may be due to the fact that the lactose preparations used only differed slightly in this respect.

Conclusions

A consequence of the extensive mixing attained by fluidization is that the diameter of the wetted surface area has no essential influence on granule size and size distribution. Only at extremely low values of spray angle were changes in granule size observed. In practice it is sufficient to maintain a combination of nozzle height and spray angle that brings about a proper wetting of the bed surface, i.e. a combination in which no risk of clogging the nozzle orifice or the outlet air filter or of wetting the wall of the apparatus exists.

It was shown that the surface area and the water absorption properties of the starting materials essentially influence the granule growth. When flow rate and quantity of binder solution are chosen the properties of

Table 3. The influence of starting materials and nozzle air flow (Nm^3/h) on granule size (the upper values) and geometric standard deviation (the lower values).
Liquid flow rate: 150 g/min.
Inlet air temperature: granulation phase 40° C
drying phase 60° C

		Fine-crystalline lactose						Crystalline lactose					
		8 Nm^3/h			10 Nm^3/h			8 Nm^3/h			10 Nm^3/h		
		20 %	50 %	80 %	20 %	50 %	80 %	20 %	50 %	80 %	20 %	50 %	80 %
Maize starch	20 %			214 µm 2.01			165 µm 2.01			220 µm 1.92			161 µm 1.86
	50 %		123 µm 2.28			101 µm 2.25			145 µm 2.41			111 µm 2.05	
	80 %	90 µm 2.29			90 µm 2.36			99 µm 2.50			87 µm 2.11		
Potato starch	20 %			242 µm 1.92			165 µm 1.90			228 µm 1.83			185 µm 1.72
	50 %		165 µm 2.20			126 µm 2.01			160 µm 1.96			155 µm 1.84	
	80 %	155 µm 2.13			137 µm 2.05			170 µm 2.16			148 µm 1.99		

Table 4. The surface area in m^2 of 15 kg of varying mixtures of starch and lactose estimated on the basis of the particle size distribution (Fig. 1).

		Fine-crystalline lactose			Crystalline lactose		
		20 %	50 %	80 %	20 %	50 %	80 %
Maize starch	20 %			2,160			1,800
	50 %		3,150			2,925	
	80 %	4,140			4,050		
Potato starch	20 %			1,560			1,200
	50 %		1,650			1,425	
	80 %	1,740			1,650		

the starting materials should be considered in order to obtain an adequate granule size. For a complete investigation of the influence of starting materials further experiments using hydrophobic starting materials are necessary.

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