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EFFICIENCY INCREASE BY TRANSFER OF A TWO-STEP PROCESS TO A ONE-POT FLUID BED GRANULATION

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ABSTRACT

Traditionally, pharmaceutical granulates are manufactured by spray agglomeration in a mixing apparatus. In the past, the wet granulates were dried by time consuming tray drying. Nowadays, fluid bed drying is the preferred procedure. The application of two consecutive steps in different apparatus is still connected with material loss and contamination risk for which reason both agglomeration and drying step should be performed in one and the same apparatus.

The aim of the investigation was the transfer of a two-step process consisting of a spray mixing agglomeration followed by fluid bed drying of a commercial drug product to a one-pot procedure in a batch laboratory fluid bed apparatus. Therefore, a fluid bed granulator and dryer GPCG 1.1 (Glatt Corp., D-Binzen) was used. To optimize the process parameters of spray agglomeration spray rate was varied between 20 and 40 g/min, all other process parameters were kept constant. Process parameters of the laboratory drying step referred to the production process. Dry granulates were compressed to tablets. Evaluation criteria were the maintenance of stable and reproducible processes, acceptable yields and high granulate and tablet quality according to market product specification and pharmacopoeia.

Best products were received with high inlet air temperature (80°C), high spray rate (30-40 g/min) and an additional water spraying. Without interruption of the fluid bed process the wet agglomerates were dried. Granulate yields were above 90%. The whole granulation process was stable and reproducible. Granulate properties fulfilled the demands of the market product specification and pharmacopoeia. Particle size was slightly increased with increasing spray rate compared to the production process, but there was no significant influence neither on granulate nor on tablet properties. The two-step granulation process with different equipment was successful transferred to a one-pot fluid bed process saving process time and equipment.

Key Words: Fluid bed granulation and drying, one and two step processes, process transfer

INTRODUCTION

Granulation is one of the most important unit operations in the production of solid pharmaceutical oral dosage forms [1]. The main objectives for granulation of powders are to reduce the bulk volume for better handling and therefore to improve the flow properties and to achieve mixture homogeneity and API (active pharmaceutical ingredient) content uniformity [2]. Another reason for granulation is the reduction of health hazards deriving from handling fine dusty powders, especially strong potent APIs [3].

In pharmaceutical production scale the batch high shear granulation (spray mixing) and the batch fluid bed granulation are common processes, but actually in most cases two-pot processes are performed in the production of granulates [2]. In the present case, for the manufacturing of a film tablet (market product) by compression of granulate the powder mixture is agglomerated in a high shear mixer. The wet agglomerate is completely sieved and transferred to a fluid bed granulator for drying. The transfer of the interim product is accompanied by material loss and insufficient yield, temporary blocking of the sieve, furthermore the risk of cross contamination and difficulties in the control of both interacting apparatuses arise. The combination of the unit operations powder mixing, wet agglomeration and drying in only one fluid bed apparatus should offer the possibility to reduce or neglect the disadvantages deriving from the actual two-pot procedure and to reduce process time and energy consumption [4]. A direct transfer of the process from two-pot to single-pot mode in production scale with pilot batches is not recommendable because of the very expensive API.

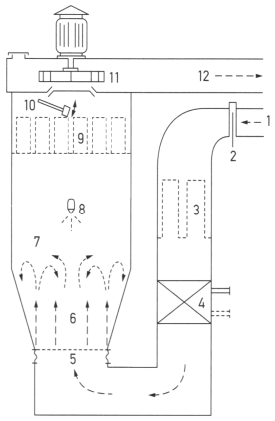
Therefore, the aim of the investigation was the development of a batch single-pot fluid bed granulation process in laboratory scale maintaining the specified granulate and tablet properties. To develop and optimize the fluid bed wet agglomeration process the actual production process parameters and experiences with similar formulations in laboratory fluid bed granulation processes were taken into consideration. Both agglomeration and drying processes were investigated due to homogeneity and stability of the fluid bed, material precipitation, yield and process time. Granulates were characterized by flow properties, particle size and residual moisture.

Granulates were mixed with lubricant and compressed to tablets. The tablet properties API content and release, weight uniformity, disintegration time and hardness were investigated and compared to the specification of the market product and evaluated according to Pharmacopoeia demands. A successful single-pot granulation with granulate and tablet properties meeting the acceptance range should give the supposition for the scaling-up to the production process.

Problems in the conversion from high shear granulation to fluid bed granulation may arise from the differences in the mode of solid agitation, acting shear forces and granule growth. High shear granulators consist of a spherical process chamber equipped with impeller and chopper. Powder components are intensively mixed by the impeller with high shear forces and pressure. The granulation liquid is sprayed from the top or vertically onto the powder bed leading to particle wetting and agglomeration. High shear granulates show a relatively high density compared to fluid bed granulates. The chopper prevents the formation of too large lumps. The spray process is stopped before super-wetting the powder mixture occurs. Normally, the wet agglomerate is discharged, completely sieved with high mesh size and dried in a separate process, e.g. tray dryer or fluid bed dryer [4-6].

Fluid bed granulators and dryers (Figure 1) consist of a conical process chamber (6), expansion chamber (7) and filter housing (9) one upon the other. By process air (1) the powder particles at the air distribution plate (5) are accelerated and a fluid bed is generated (6). The binder solution is sprayed in top spray modus (8) into the centre of the fluid bed opposite to the air flow. The particles agglomerate and the solvent of the granulation liquid is evaporated simultaneously under the influence of hot process air. Shear forces and pressure onto the particles and agglomerates in the fluid bed are lower than at high shear granulation leading to products with lower density compared to high shear mixing granulates. When the agglomerate size meets the desired value the spray process is stopped and the drying process follows without interruption of the fluid bed. The drying process may be controlled in-line by exhaust air humidity and off-line by withdrawal of samples. Fluid bed granulates as well as high shear granulates are received as irregular, polydisperse products [5-7].

Fig. 1. Main principle of a fluid bed granulator and dryer (with courtesy of Glatt Co., D-Binzen)



1 process air, 2 air-inlet damper, 3 air-inlet filter,
4 process air heating, 5 air distribution plate,
6 process chamber, 7 relaxing zone, 8 spray nozzle,
9 product filter in the filter housing, 10 filter shaking
11 ventilator for process air generation, 12 exhaust air

MATERIAL AND METHODS

Material

The commercial drug product is a film tablet. In this investigation the coating process is neglected, only granulation and tablet core compressing are under consideration (Table 1). For wet granulation, an aqueous solution (purified water) is used. All substances were of pharmaceutical grade [8].

Table 1. Market product tablet core formulation without film

API
Maize starch
Magnesium carbonate, heavy
Hyprolose
Sodium dodecyl sulfate
Sodium carboxymethyl starch type A
Magnesium stearate

Methods

Fluid bed granulation and drying

The fluid bed granulation and drying process was performed in a batch laboratory fluid bed granulator GPCG 1.1 (Glatt, D-Binzen) with 24'' conical expansion chamber of height 600 mm, upper diameter 300 mm and lower diameter 140 mm (Figure 2). The expansion chamber is equipped with control windows, sample slide 150 mm above the bottom and temperature sensor. A ring (inner diameter 140 mm, outer diameter 210 mm, height 65 mm) at the lower end of the chamber carries a narrow wire-gauze.

The tower of bottom equipment, process chamber, expansion chamber and filter housing with exhaust air tube are vertically positioned on a table and tightly fitted by a hydraulic clamping system. The control unit is mounted on the right side of the table. The binary spray nozzle (Düsen-Schlick, D-Untersiemau/Coburg) of diameter 1.0 mm is used in the top spray modus and located in the centre of the process chamber and also in the centre of the fluid bed, respectively. Process air is generated by a ventilator situated in the exhaust air channel, heated and sucked through the wire-gauze at the bottom into the process chamber generating a fluid bed of the original powder particles. The humidity of the process air is influenced by the actual room climate (temperature and humidity). The granulator was preheated without material just before the granulation process over 10 minutes [7].

Figure 2. Laboratory fluid bed granulator GPCG 1.1 (Glatt, D-Binzen)

Compression into tablets

Granulates were sieved (1200 µm), mixed with lubricant in a cube mixer (KB 15, flanged to basic drive 402, Erweka, rate of rotation 200 r.p.m., 20 min). The pressing material was compressed into tablets of required weight 212 mg with a rotary press (Kilian S 100, D-Köln).

Granulate characterization

Residual moisture of granulates was measured with a Halogen Moisture Analyzer (HG 53, Mettler-Toledo, CH-Greifensee), granulate shape and structure were investigated by stereo light microscope (Olympus SZ 61, Olympus Co.) particle size was measured offline by analytical sieve machine (AS 200 basic, Retsch, D-Haan, amplitude 50%, duration 10 min), d_{50} was calculated by software 'EasySieve' (Retsch).

Flow properties were measured according to Ph.Eur. methods [8], bulk and tap density (ρ_b, ρ_t) tap volumeter (SVM 102, Erweka, D-Heusenstamm) and compressibility index (CI) was calculated according to

$$CI = (\rho_t - \rho_b) * 100 / \rho_t) \qquad \text{Eq.1}$$

Flow time (100 g) and angle of slope were measured with flow tester (PTG S3, Pharmatest, D-Hainburg).

Tablet characterization

Weight uniformity was investigated with an analytical balance, hardness with a hardness tester (PTB-411 Pharmatest), friability with a friability tester (PTF 10, Pharmatest), disintegration with a disintegration tester (PTZ Pharmatest, 750 ml purified water, 37°C) and drug release with dissolution tester (PT2, Pharmatest, volume 900 ml, 37°C, paddle speed 100 r.p.m.) according to Ph.Eur. [8]. The API content was measured by UV spectroscopy (Spekol 1300, Analytik Jena, D-Jena, wavelength 274 nm, quartz cell 10 mm).

RESULTS AND DISCUSSION

The process parameters batch size, granulation liquid amount and spray rate were scaled down from high shear production to laboratory fluid bed mode (Table 2). Atomization air pressure was kept constant. Process air temperature was increased in the fluid bed process due to simultaneous processing of agglomeration and drying. Spray rate was varied between 20-40 g*min^{-1}, process air volume was adjusted to increasing agglomerate weight and humidity by variation in the range 45-70 m³*h^{-1} to maintain fluid bed. For comparison, the production process parameters are listed.

Table 2. Granulation process parameters high shear production and fluid bed laboratory scale

Granulation mode	**High shear**	**Fluid bed**
Scale	**Production**	**Laboratory**
Process air volume [m³*h^{-1}]	-	45-70
Process air temperature [°C]	22	80
Atomization air pressure [bar]	-	2.0
Batch size [kg]	298	1
Granulation liquid [kg]	109	0.355
Spray rate [kg*min^{-1}]	~13	0.020-0.040

For fluid bed drying, process air temperature and product temperature at the end of drying were kept constant (Table 3). Process air volume was scaled down. Residual moisture was advised below 4%.

Table 3. Drying process parameters of fluid bed production and laboratory scale

Drying mode	**Fluid bed**	**Fluid bed**
Scale	**Production**	**Laboratory**
Process air volume [m³*h^{-1}]	1.500-3.000	45-70
Process air temperature [°C]	70-95	80
Product temperature at the end of drying [°C]	35-50	35-40
Residual moisture [%]	2-4	<4

At spray rate 20 g*min^{-1} the granulation process was not successful. Agglomeration did not take place, and at the end of the final drying process the initial powder particles were present. It was concluded that the granulation liquid amount either the binder concentration (hyprolose) were not sufficient. For this reason, two parameters were changed for process optimization: in first trials directly after the spraying of the whole amount of binder solution an equal amount of water (355 g) was sprayed to increase the granulation liquid supply and therefore to improve the chance of agglomeration. In a second trial the amount of additional water was nearly doubled (600 g). Last not least, the additional water spraying (355 g) was combined with doubling of the hyprolose concentration of the granulation liquid to increase sticking and adhesive properties. The spray rate was adjusted in the range 20-40 g*min^{-1}. The other process parameters were kept constant.

At additional water supply, both fluid bed granulation processes at spray rate 30 and 40 g*min^{-1} were stable (Table 4). Mixing of the initial powder components, wet agglomeration and drying of the wet agglomerates to receive final granules with residual moisture below 5% were performed without interruption of the fluid bed. Homogeneous granulates were received and only small material amounts were lost by precipitation at the inner wall of the process chamber and possibly at the exhaust air filter. Yield was about 90% (Table 4).

Granulation process time was 30-45 min in dependence of spray rate, and drying time was comparable short (5 min). At increasing spray rate granulate particle size raises due to acceleration of agglomeration process. The process time and therefore the probability of granule collision and disintegration are reduced. Bulk density values are similar but compressibility index and angle of slope of batch 40 g*min^{-1} indicate lower densification and better flow properties resulting from higher particle size compared to batch 30 g*min^{-1}. The strong reduction of flow time with particle size increase gives hints to an extreme flow improvement.

Table 4. Granulate properties with additional water amount 355 g

Spray rate [g*min^{-1}]	**30**	**40**
Yield [%]	93	91
Residual moisture [%]	2.7	1.8
d_{50} [µm]	75	126
Bulk density [g*ml^{-1}]	0.54	0.56
CI [%]	18	15
Flow time 100 g [s]	43	5
Angle of slope [°]	24	26

Granulates with additional water amount of 600 g were also received as homogeneous, polydisperse and white products but with increased particle size compared to the batches with only 355 g additional water. Under the light microscope large agglomerates as well as fine separate particles are visible (Figure 3). The trend of particle size increase with ascending spray rate is confirmed (Table 5). The combination of high spray rate (40 g*min^{-1}) and large water amount (600 g) leads to highest particle size (892 µm). Bulk density, compressibility index and angle of slope of three batches with spray rate 30, 35 and 40 g*min^{-1} differ only slightly, and a trend with increasing spray rate is not detected. Vice versa, flow time is significantly reduced with increased particle size.

Figure 3. Microphotograph of laboratory fluid bed granulate (spray rate 35 g*min^{-1}, additional water 600 g)

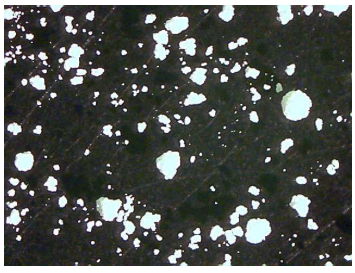


Table 5. Granulate properties, additional water amount 600 g

Spray rate [g*min^{-1}]	**30**	**35**	**40**
Yield [%]	97	91	97
Residual moisture [%]	3.0	3.1	1.9
d_{50} [µm]	150	298	892
Bulk density [g*ml^{-1}]	0.53	0.50	0.46
CI [%]	12	14	14
Flow time 100 g [s]	25	4	5
Angle of slope [°]	25	27	29

The content of hyprolose in the granulation liquid was doubled and combined with an additional water spraying of 355 g, spraying rate amounts 20 and 30 g*min^{-1} (Table 6). The combination of both process changes was successful. Granulates were received with satisfactory particle size and flow properties. But one has to take into account that the doubling of binder amount means a change of product formulation what requires a change of the marketing authorization dossier so that the process variant with only water addition should be preferred.

Table 6. Granulate properties, additional water amount 355 g and double binder amount

Spray rate [g*min^{-1}]	**20**	**30**
Yield [%]	97	95
Residual moisture [%]	2.3	2.4
d_{50} [µm]	94	126
Bulk density [g*ml^{-1}]	0.56	0.56
CI [%]	16	13
Flow time 100 g [s]	46	11
Angle of slope [°]	29	26

Granulate of the market product is specified due to residual moisture (2.0-4.0%) and bulk density (0.45-0.80 g*ml^{-1}). Residual moisture scatters between 2.3 and 3.0%, bulk density between 0.50-0.56 g*ml^{-1}. The demands are fulfilled by all granulates independent of spray rate, granulation water addition and doubling of binder amount. There is no significant tendency of the product parameters bulk density, compressibility index and angle of slope in dependence of spray rate, binder concentration or additional water spraying. As expected, particle size and flow time increase at higher spray rate. The low extend of densification in the treatment with the tap volumeter is similar for all lots and leads to compressibility indices 12-18% indicating good to satisfactory flow properties [8]. Angle of slope values 24°-29° and flow time values of 4-11 s correspond to excellent flow properties [8]. Higher flow time may derive from electric charge or moisture.

Granulates with too large particle size (batches of spray rate 40 g*min^{-1}) were not compressed into tablets and neglected from the further investigation. The compression process came about without striking features. The tablets were received in desired shape and with smooth surface. All tablet batches compressed from granulates with spray rate 20, 30 and 35 g*min^{-1} fulfill the demands of the market product specification and Ph.Eur. (Table 7 and 8). Mean weight differs from the required value by maximum 7 mg what is far below the acceptance range of ±5%. Coefficient of variation (CoV) of mean weight does not exceed the conventional acceptance value of 4%, and the pharmacopoeia demand of minimum 18 tablets (n=20) within a range of ±7.5% is fulfilled. Hardness values are in the range 40-70 N. Also friability meets the demand of maximum 1%. Disintegration time was in all cases below the limit of 15 min [8], and drug release surpasses the value of 85% after 30 min.

Table 7. Tablet properties of granulate batches spray rate 20, 30 and 35 g*min^{-1}, (a) Ph.Eur. demand, (b) product specification

Spray rate [g*min^{-1}]	**Specification**
Add. water amount [g]	
Mean weight [mg]	212 (a)
CoV of mean weight [%]	<4
Hardness [N]	40-70 (b)
Friability [%]	<1 (a)
Disintegration time [min]	<15 (a)
Drug release 30 min [%]	85 (b)

Table 8. Tablet properties of granulate batches spray rate 20, 30 and 35 g*min^{-1} (n) normal, (d) double

Spray rate [g*min^{-1}]	**30**	**30**	**35**	**20**	**30**
Add. water amount [g]	**355**	**600**	**600**	**355**	**355**
Binder concentration [%]	**n**	**n**	**n**	**d**	**d**
Mean weight [mg]	215	210	209	219	215
CoV of mean weight [%]	0.84	0.83	1.5	0.89	0.66
Hardness [N]	57	56	86	66	63
Friability [%]	0.2	0.2	0.2	0.17	0.17
Disintegration time [min]	5	5	6	9	8
Drug release 30 min [%]	94	93	93	96	95

CONCLUSION

The wet granulation and drying process of a market product performed in two different production units (high shear wet granulator and fluid bed dryer) was successful transferred to fluid bed granulator in laboratory scale. Granulates were manufactured by mixing of the initial powder components, wet agglomeration and drying without process interruption. Additional water spraying immediately after binder solution spraying was necessary to increase the supply with granulation liquid and to guarantee a sufficient particle agglomeration. The parameters of the partial processes fluid bed agglomeration and drying were in the same range as those for similar formulations. Granulate and tablet properties fulfilled the demands of the market product specification and Ph.Eur. The results of the investigation in laboratory scale give the base for a scaling-up of the single-pot granulation process into production scale.

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NOMENCLATURE

Greek letters

ρ_b bulk density [g*ml^{-1}]
ρ_t tap density [g*ml^{-1}]

Abbreviations

CI	Compressibility index
CoV	Coefficient of variation (of mean weight in this case)
d_{50}	Arithmetic mean diameter
Ph.Eur.	European Pharmacopoeia
UV spectroscopy	Ultraviolet spectroscopy

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