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Flow Characteristics Optimization of Corn Starch and Microcrystalline Cellulose Mixture by Wet Granulation

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1. Introduction

Wet granulation is a size enlargement operation which is widely used in pharmaceutical field to modify the powder properties. In fact, the friability and hardness of the final solid dosage form (i.e., tablets), may be significantly improved if initial powders are prior granulated to the desired size and shape.
In this optic, a parametric study was carried out with two excipients, ***microcrystalline cellulose*** and ***corn starch,*** two excipients generally used for tabletting but with poor flow characteristics. A laboratory scale mixer granulator Lödige of 4 litres capacity equipped with blades has been used to achieve mixing and wet granulation. The effect of some parameters such as excipients proportions, binder quantity, rotational speed blades, drying temperature, size aperture of screens and residual humidity were investigated. The morphology of obtained granules was visualized by optical microscope (OM) and scanning electron microscope (SEM).
Experimental results showed that increasing rotational speed, drying temperature and size screen with reduced value of residual moisture, lead to obtain dense granules of raised size, tightened, with a narrow granulometric distribution and with excellent flow properties. The compacting test gave tablets with satisfactory hardness and friability which are suggested by European Pharmacopoeia.

2. Materials and experimental procedure

2.1 Materials

Corn starch (Roquette pharma) and microcrystalline cellulose (Polypharma tech. Scienc. GMBH) were the products used in the granulation experiments. Prior, the particle size of the powders was measured using a Malvern Mastersizer analyzer 2000 and flow properties were evaluated by determining Carr's index and Hausner ratio values. Table 1 provides physical characteristics of the primary powders. Demineralised water has been used as liquid binder to achieve wet granulation.
These two powders have poor flowability as it revealed by Carr's index and Hausner ratio values. Hausner ratio of 1,25 is regarded to represent the threshold between free flow and no flow.

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Table 1: Physical properties of solid particles

Solid material	Corn starch	MCC (Avicel PH101)
Median mean size $d_{50\%}$ (μm)	25,05	75,95
Size distribution span, $d_{90\%}$ - $d_{10\%}$ (μm)	61,1 - 11,28	188,65 - 21,87
Span	1,942	2,198
Bulk density (Kg/m^3)	430	400
Taped density (Kg/m^3)	570	540
Carr's index (%)	26,05	26,80
Hausner ratio	1,35	1,36

2.2 Equipment

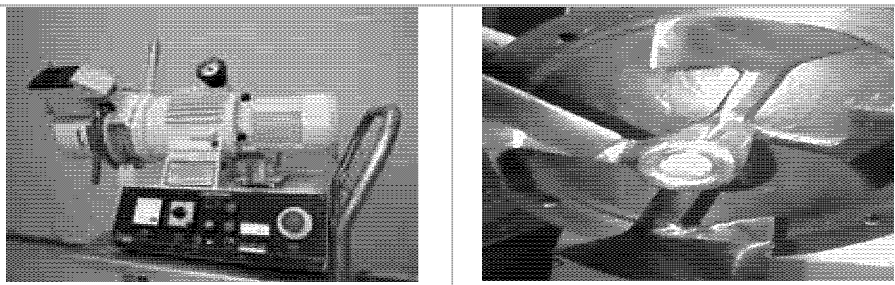
The experimental apparatus, showed by figure 1, was a laboratory scale mixer granulator Lödige M5 of 4 litres capacity which works at a batch mode.

The mixer granulator is essentially composed by the following elements:

a removable drum with a rectangular opening, interchangeable lids with safety locking and a removable projector device.

Mixing operation is achieved in the drum where exists a shaft fitted with projecting blades shaped as plough shears.

In this granulator, axial and radial trajectories of each solids particle cross. The grains are frequently reflected on the drum walls and mixer tools where they are again taken and accelerated. Thus, the turbulence caused by the action of tools on the totality solids mixture prevents the formation of "dead zones" and ensures a fast and complete mixing.



(a) (b)

Figure 1: (a) Laboratory scale mixer granulator Lödige M5, (b) granulator blades

2.3 Experimental procedure

The experimental procedure was to introduce excipients in the granulator, to fully mix them and then to add progressively water by pulverisation at constant flow rate (8,45 mL/s). The granulation step was held at constant speed rotational impeller. The obtained granules were then dried in a hot-air oven at a constant temperature until residual humidity attained desired value. After, granules products were passed through an oscillating granulator fitted with screens of different sizes.

In a first step, preliminary tests were carried out to determine proportions of excipients as well as quantity of water which is necessary to completely wet powder mixtures. According to previous works (Dukic´-Ott et al., 2009; Rowe et al., 2008), the chosen operating conditions of preliminary tests are summarised in table 2.

Table 2: Operating conditions of preliminary tests

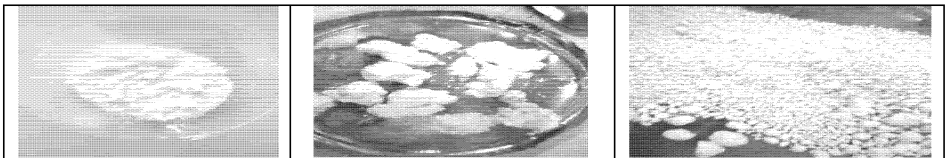
Test no.	Powder mixture quantity (g)	Water volume (mL)	Excipients proportions [MCC ; Corn starch] (w/w%)	W_{liquid}/W_{solids} (w/w)
1	500	400	[80%; 20%]	0,80
2	500	400	[70% ; 30%]	0,80
3	500	570	[70% ; 30%]	1,14
4	500	520	[70% ; 30%]	1,04

The first test led to obtain grains having very poor proprieties of use as requested. The grains were too friable because the quantity of binder was insufficient to favour solid bridges formation and achieve particles agglomeration, as reported by Jimenez (2007) and Benali (2009).

With a mixture [70% MCC; 30 % Starch] as recommended by Dukic´-Ott et al., (2009) and the respectively two water volumes (400 mL ; 570 mL), the granulation lead for the first case to very friable grains, which crumbled easily in hand. The quantity of water was not sufficient to ensure a complete wetting of particles so that the interstices between the particles were filled until saturation and so to get grains with more resistance.

On the other hand, test no. 3, carried out with 570 mL of water lead to a pasty state indicating that the quantity of water is too excessive and the particles were over-wetting as mentioned by Rondet (2008) which indicates that over an optimal liquid quantity pasty regime is attained after agglomerates regime.

Test no. 4, conducted with 520 mL of water, was conclusive; particle agglomeration occurred by giving strong grains with a poor friability as visualised by figure 2.



(a) Absence of grains *(b) Over-wetting phenomenon* *(c) Granulation*

Figure 2: Products of preliminary tests granulation

3. Results and discussion

3.1 Influence of rotational speed impeller

3.1.1 On granulometry

The influence of rotational speed impeller was examined through three tests carried out under the same operating conditions of drying temperature (50°C), residual moisture (3%) and with respectively 129,5; 210,5 and 283,5 rpm for rotational speed impeller.

Figure 3 (a) illustrates the mean diameters d_{10} ,d_{50} and d_{90} evolution with increasing rotational speed. It appears, in the one hand that, rising rotational speed favourite considerably growth grains diameter and in the other, granulometric distributions become narrower as indicated by span values (b). As reported by Saleh et al. (2005), this tendency is explained by the fact that with increasing rotational speed, both the collision frequency between granules and the collision energy increase and therefore nucleation stage take place more rapidly and more efficiently. This is well illustrated by d_{10} values indicating that size particles of fines population is significantly enhanced when rotational speed augments.

However, for larger size granules which are wet and have poor résistance another phenomenon appears after their growth step: it is breakage phenomenon which occurs when stress due to mechanical agitation is important. These considerations are confirmed by d_{90} values which are not too markedly affected by the speed because breakage takes place.

Also, as shown in figure 4, with increasing rotational speed, particles present more uniformity in shape and better packing, which indicate that grain structure depends closely by rotational speed.

This behaviour was observed by Rahmanian, et al. (2009), Rondet (2008) which explained it by the fact that the increase of rotational speed increases contact surface and the collisions frequency between particles, by expelling the liquid of agglomerates. Porosity is then reduced by favouring the densification phenomenon which leads to tightened grains in size.

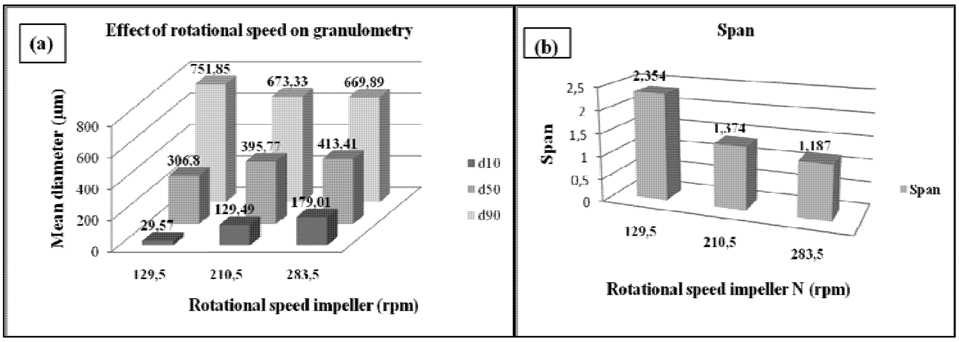
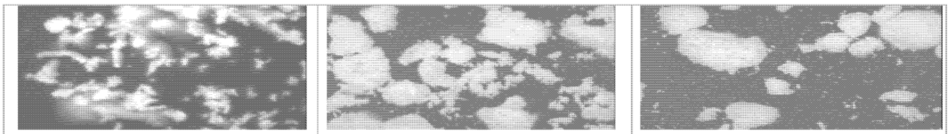


Figure 3: Rotational speed effect on (a) granulometry, (b) granulometric distribution



(a) N= 129,5 rpm (x100) (b) N= 210,5 rpm (x50) (c) N= 283,5 rpm (x50)

Figure 4 : OM images of granulated particles obtained with different rotational speed

3.1.2 On Flowability

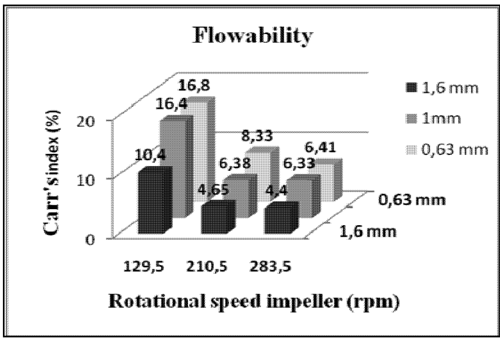
The results on figure 5 show clearly that Carr's index decreases when rotational speed increases, and as flow facility is inversely proportional to Carr's index , then it appears that higher the rotational speed, higher the flowability.

3.2 Influence of drying temperature

The tests were carried out at the same speed rotational impeller (283,5 tr/min) and under three oven temperatures: 30°C, 40°C and 50°C until reaching a residual humidity of about 3%. The experimental results giving humidity evolution of the grains versus time permit to determine drying rate for the three temperature values figure 6.

As indicated by results, it is possible to note that drying time of grains at 40°C is twice more significant than that necessary at 50° C. With a temperature of 50 °C, drying rate increased more quickly during a time 5 times less significant than that of 40°C.

Figure 7 shows that Carr's index decreases with increasing temperature. This means that an increase in temperature lead to an improvement of grains flow. The disappearance of liquid bridges is caused by the penetration of the heat flow inside the pores what decreases the flexibility of the wet grains, by progressively reducing their porosity to conduct at more dense structure. We observed also that increasing temperature led to increase hardness of grains surface.



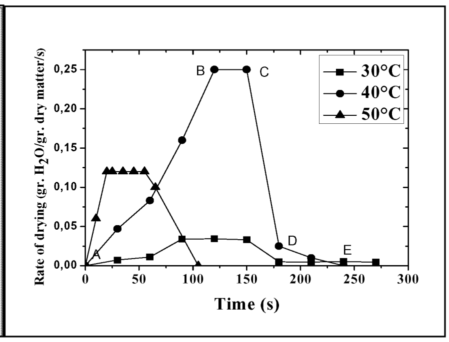


Figure 5: Effect of rotational speed *Figure 6: Temperature effect on drying rate*

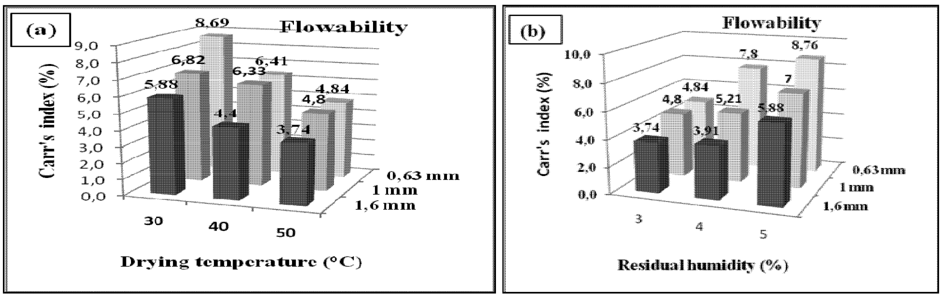


Figure 7: Effect of drying temperature (a) and residual humidity (b) on flowability

3.1 Compressed form

In order to test grains powder produced, we carried out a compression to obtain tablets. These tablets had hardness of 16,2 Kp (>7 Kp) and friability of 3.10^{-4} %. These values indicate that compression aptitude was largely improved after granulation.

Conclusion

According to obtained results, it appears that the increase of rotational speed, drying temperature, size calibration, and the reduction of residual humidity lead to obtain dense grains of larger size, with narrow granulometric distribution and with better flow properties. The experimental conditions which conducted to have a product with optimal qualities suggested by European Pharmacopoeia are: Excipients mixture [30 %; 70%], water-powder ratio of 1,04, rotational speed of 283,5 tr/min, drying temperature of 50 °C, residual humidity of 3% and a calibration of 1,6 mm.

Wet granulation of excipients presenting poor flow properties improved tablets quality.

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