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STUDY THE EFFECT OF PROCESS VARIABLES IN FLUID BED GRANULATION ON THE PHYSICO-CHEMICAL PROPERTIES OF GRANULES

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ABSTRACT

The purpose of this research was to improve the granulation efficiency and the final granule characteristics for the any kind of the material that is to be granulated via FBG process. The fluid bed granulation process is an influenced by various processing parameters like atomization pressure, binder addition rate, in let temperature etc. These process variables largely affect the granulation efficiency and the final granule characteristics. The effect of starting materials on granule properties was previously studied. The aqueous solution of 5% PVP K-30 was used as a binder and sprayed on lactose monohydrate bed. A full factorial design was applied to optimized the granulation process variables like inlet air temperature, spray rate and batch size and other granule properties, namely the Carr's index, Hausner index, the angle of repose and the moisture content, were evaluated at the optimal operation conditions. Granules prepared by this technology have good flow property, good compressibility; and good flow ability with a proper adjustment of process variables. So FBG technique has its own importance for the granulation purpose in the pharmaceutical industry and technology.

INTRODUCTION: The theory and techniques of fluidization have been known for many years. Fluidized bed technique has been used in pharmaceutical industry for drying, coating, and recently granulating. Wurster (1959) first described granulation in the fluid bed. The design and operation of fluid beds for continuous production of tablet granulation was presented by Scott et al. (1964).

At the beginning of the process, gas flows through a solid bed. Starting from this initial state with a uniformly increasing airflow velocity, a point is reached at which the particles start moving and the product batch is fluidized. This point is referred to as fluidization point and marks the beginning of fluidization. If the velocity is increased further, the particle movement also becomes more forceful. Air, which is not needed to maintain the particles in fluid state, passes through the fluid bed in the form of gas bubbles causing strong turbulence. The maximum flow rate is defined as the rate at which the particles are removed from the fluid bed by pneumatic conveyance [1, 2].

Fluidized bed granulation is a process by which granules are produced in a single piece of equipment by spraying a binder solution onto a fluidized powder bed. This process sometimes classified as the one pot system. The fluid bed granulation process has received considerable attention within the pharmaceutical Industry however other process industries such as food, agrochemical, dyestuffs and other chemical industries have adopted fluid bed granulation process to address particle agglomeration, dust containment and material handling [3].

MATERIALS AND METHODS:

Chemicals: Lactose monohydrate IP and Polyvinyl Pyrrolidone K30 was obtained from S.D. Fine chem. Ltd., Mumbai, distilled water prepared in laboratory.

Instruments: Fluid bed granulator (Cronimach machineries, Ahmadabad), Sartorious Digital moisture balance (MA 45, Signum test, 230 volts), Sieve shaker (Kevlab, Kevin Engineering Pvt. Ltd. Ahmadabad), Bulk density apparatus (DBK instruments Mumbai-60).

Experimental test matrix: The study involved a 2^3 full factorial design. The experimental test matrix was set up in order to study the binder spray rate, atomizing air pressure, batch size, inlet temperature [2, 7] (**Table 1**). The effect of atomization air pressure and binder addition rate on final granule properties was studied with mixed results and the inlet air humidity was not controlled and generally constant [2, 4].

TABLE 1: A 2^3 FULL FACTORIAL DESIGN TO STUDY THE EFFECT OF FLUID BED GRANULATION PROCESSING VARIABLES ON PHYSICAL PROPERTIES OF GRANULES

Experiment Run	Binder spray rate (ml/min)	Batch size (g)	Inlet air Temperature (^{0}C)	Binder Atomizing Pressure (kg/cm^2)
B_1	3	60	60	0.15
B_2	5	60	60	0.15
B_3	3	100	60	0.15
B_4	5	100	60	0.15
B_5	3	60	70	0.15
B_6	5	60	70	0.15
B_7	3	100	70	0.15
B_8	5	100	70	0.15

Preparation of lactose granules: Granules of lactose were prepared using fluid bed granulation technique. Amount of lactose as per batch size was taken and transferred to fluid bed granulator (Table 1) [5]. Afterwards the aqueous solution of a binder (5% PVP K-30) was sprayed on the fluidizing powder bed using a peristaltic pump (adjusting the spray rate). The spraying process was carried out according to the settings of the process variables for the specific run. The wetted granules were dried by fluidizing them with an inlet air temperature of 75°C. Samples were taken at regular intervals in order to measure the granule growth and the bed moisture content as the granulation progressed [6].

Characterization of Granulation Process:

Granule growth profile: The granule growth profile was obtained by plotting the mean granules diameter of each sample taken during the granulation process versus time. The mean diameter of granule was determined on a 15 gram of sample using sieve shaker and the sieves no used were 10, 20, 40, 60, 80, 100 µm [2, 6,7,15].

Granulation wetting profile: The IR moisture balance was used to measure the moisture content (Expressed as % LOD) of each sample taken during the progress of the granulation run. Percentage LOD was plotted against time to provide the wetting profile of the granulation process [2, 6,7,15].

Final granule size distribution: Using sieve shaker and a set of 6 sieves (10, 20, 40, 60, 80, 100 µm.), a 50 gm of the final product was shaken for 10 min to obtain the size distribution and the geometric mean diameter [8, 9, 10].

Bulk and tapped densities: Granules were gently poured into 50 ml graduated cylinder. The granule weight and volume were used to calculate the bulk density. Using automatic tapper, the cylinder was tapped 500 times and the new volume was used to calculate the tapped density. The bulk and tapped densities were used to determine the Carr's index, and Hausner's ratio. The Carr's index and Hausner's ratio value was used to categorized the powder flow. The Carr's index and Hausner's ratio were calculated according to following equations [8, 9];

$$\text{Carr's Compressibility index } (\%) = (\rho 2 - \rho 1) / \rho 2 \times 100.$$

$$\text{Hausner's Ratio} = vb/vt \quad \text{or} \quad \rho_t / \rho_b$$

Where ρ1 & ρ2 are the Apparent and Tapped densities of the material, vb & vt are the bulk and tapped volumes of the material and ρ_t & ρ_b are the Tapped and bulk density of the material respectively.

RESULTS AND DISCUSSION: The Content of binder spray rate (X_1), Batch size (X_2), and inlet temperature (X_3) were chosen as independent variables in a 2^3 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the response.

$$\mathbf{Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{123}X_1X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2}$$

Where Y is the dependent variable and b_0 is the arithmetic mean response of the 8 runs and b_1 is the estimated coefficient for the factor X_1. The main effect (X_1, X_2 and X_3) represents the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2, X_2X_3, X_1X_3, and X1X2X3) show how the response changes when 3 factors are simultaneously changed. The polynomial terms x_1^2 $x_2^2$and x_2^2 are induced to investigate nonlinearity. The polynomial equation can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative) [11]. The response variables in this study are the Mean Granules size (Y_1), friability (Y_2) and bulk density (Y_3). In order to determine the effect of the operating variables on the response variables, a set of designed experiments was performed. For that two binder spray rate (X_1), two Batch size (X_2), and two inlet temperature (X_3) were selected to perform a two level factorial design for the present study. Each of these operating variables was selected at lower and upper levels. The results were statistically analyzed. The regression results were given in **Table 2**.

TABLE 2: VALUES OF CORRELATION OF VARIABLES

Y	b_0	b_1	b_2	b_3	b_1b_2	b_2b_3	b_1b_3	R^2
MGS	462.37	27.625	-14.125	-6.875	5.625	-0.875	2.875	0.9946
FR	0.7225	-0.1375	0.0825	0.035	0.0075	0.005	-2.3919	0.9990
BD	0.5697	-0.0215	0.01275	0.00775	0.0005	0.00025	-0.002	0.9967

Effect of binder addition rate: Using the 5% w/w PVP K-30 binder solution addition rates of 3 and 5 ml/min were tested in this experimental section. At the slower addition rate (3 ml/min), it was observed that effective evaporation of the solvent was obtained such that there was little influence on the moisture levels (Fig. 3). At these low wetting levels, the granule growth was primarily controlled by the amount of PVP K-30 added.

At the higher addition rate (5ml/min), wetting profile of the granules was higher so the granule growth can be controlled by the addition of the PVP K-30. Fig. 1, Fig. 2 and Fig. 3 illustrate the effect of binder solution spray rate on the Mean granules diameter and percentage retained on the various mesh screens (Fig. 5). Granules growth was depended on the binder availability at the surface. If too much liquid is added or the evaporation of the liquid is not adequate then this results in an increase of the powder bed moisture content. Above certain powder bed moisture content the powder bed becomes over wetted and defluidizes [2, 12, 13]. As summarized higher spray rate allows a greater number of droplets to be sprayed onto the starting material per unit time. This resulted in an increased number of liquid bridges and hence larger granule size. With a lower spray rate, binder solution evaporated more rapidly and binding of particles was reduced. In addition, the longer granulation time as a result of a low spray rate exposed granules to attrition forces resulting in smaller granules.

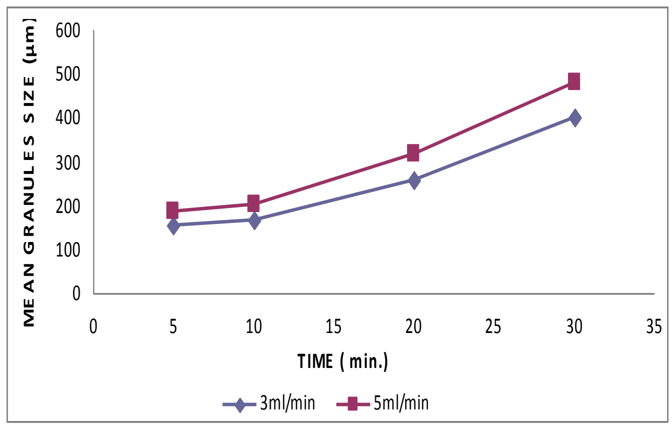

FIG. 1: MEAN GRANULES SIZE VS TIME FOR DIFFERENT SPRAY RATE FOR 5% W/W PVP K-30 BINDER SOLUTION

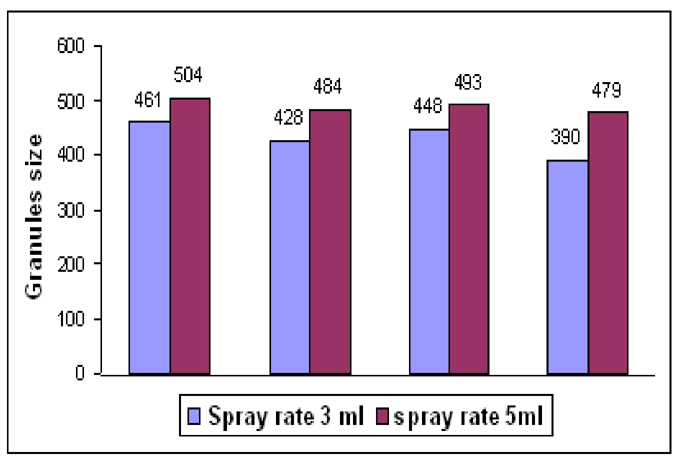

FIG. 2: MEAN GRANULES SIZE VS TIME FOR DIFFERENT SPRAY RATE FOR 5% W/W PVP K-30 BINDER

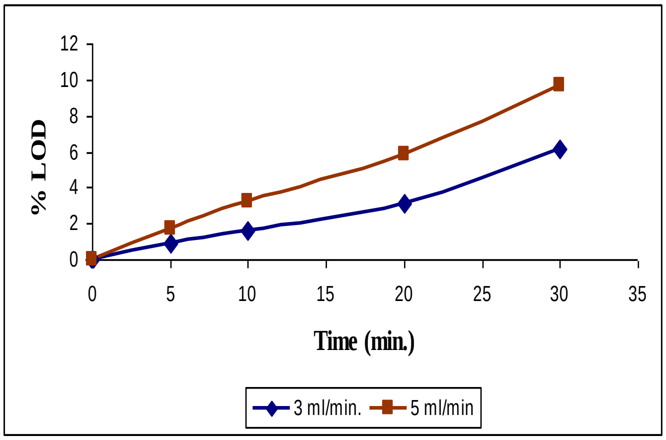

FIG. 3: % LOD VS TIME FOR DIFFERENT SPRAY RATE FOR 5% W/W PVP K-30 BINDER SOLUTION

Effect of inlet temperature: Evaporation of liquid depends on the inlet airflow rate and the inlet air temperature if the inlet temperature is so high that the evaporation rate is higher than the moisture migration rate needed to maintain surface wetness, the constant rate drying phase is very short. It was found that a rise in inlet temperature of fluidizing air resulted in decreased granule size and makes the granules more friable because of sudden evaporation of solvent and loose bonding occurs between particles (**Fig. 4**). Inlet temperature and spray rate are an important parameter for fluid bed granulation.

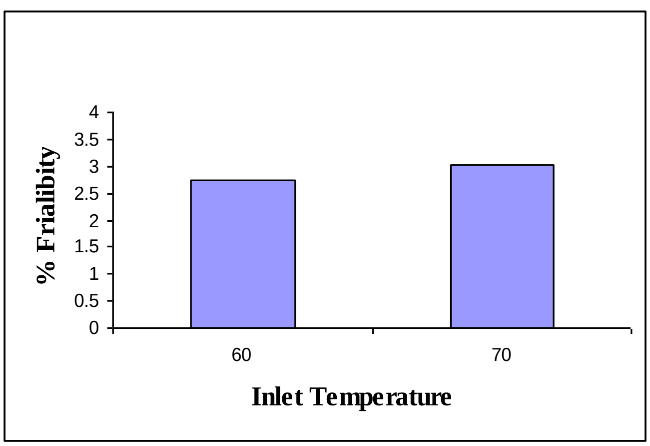

FIG. 4: EFFECT OF INLET TEMPERATURE ON % FRIABILITY OF GRANULES

Effect of batch size: From the observation it was concluded that granules formed are smaller in size in large batch size and vice versa. This may be due to availability of more droplets in small batch size in comparison with large batch size and another reason may be, attrition effect on the granules is directly proportional to fluid bed scale [2, 12, 13].

Particle size of the granulation: From the particle size determination of granules by sieve method it was concluded that Batch B7 showed maximum retention of granules on # 60 and lowest on # 20 in comparison with other batches (**Table 3 and Fig. 5**).

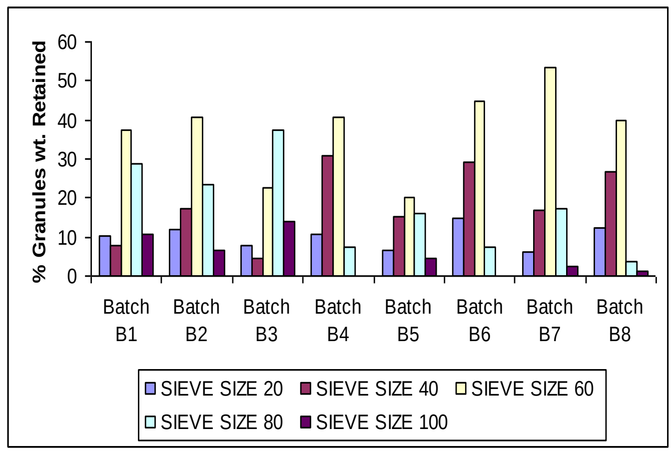

FIG. 5: PERCENTAGE GRANULES RETAINED ON VARIOUS SIEVES OF ALL BATCHES

Though, it is known that maximum retention should be on # 40 for wet granulation method. But here granules were prepared by fluid bed granulator, in which maximum retention on # 60 is considered to be best. Hence, batch B7 was found to be shown the maximum uniformity in granule size [2, 12, 13].

Effect of processing parameters on final granules characteristic:

Friability: From the observation in Table 4 it can be concluded that increase in inlet temperature and decrease spray rate, increases friability of granules; while increase in binder spray rate, decreases in atomization pressure; increase in PVP K-30 binder concentration were important factors that contribute to reduce friability of the granules.

Carr's index: The Carr's index value provided some indication of the flow of behavior of the various granulations obtained during this investigation. Granule having high Carr's index values shows the relatively poor flow than the lower the Carr's index. This was also observed and proved by measuring the angle of repose of different granulations. Observation in **Table 4 & Fig. 6** showed no major difference in the values of angle of repose and Carr's index. Batch B7 showed the lower value angle of repose and Carr's index, resulting in better flow compare to other batches, it was observed the inlet temperature, atomization pressure and binder spray rate affect the flow behavior of the granules and granules that maintained at lower binder spray rate and atomization pressure during granulation had improved flow characteristics.

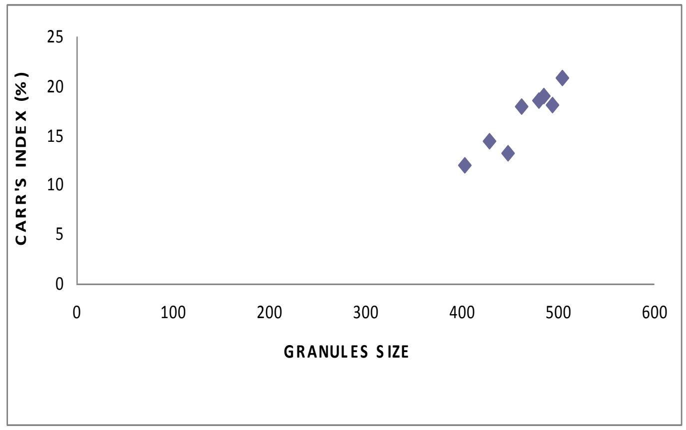

FIG. 6: THE OBSERVED GRANULES SIZE AS A FUNCTION OF THE OBSERVED CARR'S INDEX

TABLE 3: PARTICLE SIZE DISTRIBUTION STUDY OF ALL BATCHES

Sieve no	% wt. retained of granules							
	B_1	B_2	B_3	B_4	B_5	B_6	B_7	B_8
20	10.2	12.0	8.0	10.66	6.66	14.66	6.2	12.33
40	8.0	17.33	4.66	30.66	15.33	29.33	16.87	26.8
60	37.3	40.66	22.66	40.66	20.2	44.66	53.33	40.0
80	28.66	23.33	37.33	7.33	16.0	7.33	17.33	3.5
100	10.66	6.66	14.0	0.0	4.33	0	2.66	1.33

TABLE 4: SUMMARY OF GRANULATION PHYSICAL CHARACTERISTICS FOR THE DIFFERENT PROCESSING TEST

Batch	Mean Granules size (µm)	Bulk density (gm/ml)	Tapped density (gm/ml	Carr's index (%)	Hausner's ratio	Angle of repose	Friability (%)
B_1	461	0.571	0.696	17.95	1.21	30.40	0.76
B_2	504	0.528	0.667	20.83	1.26	32.00	0.46
B_3	428	0.592	0.692	14.45	1.16	30.02	0.89
B_4	484	0.557	0.688	19.04	1.23	31.40	0.64
B_5	448	0.587	0.717	13.30	1.22	30.11	0.81
B_6	493	0.542	0.677	18.13	1.24	31.60	0.53
B_7	402	0.615	0.699	12.01	1.13	29.40	0.98
B_8	479	0.566	0.695	18.56	1.22	30.69	0.71

Hausner's index: The Hausner's index gives a measure of the packing of the granules. Smaller granules tend to have greater cohesiveness due to high surface-to-mass ratio and result in greater bulk density. Therefore, the Hausner's index tends to increase with smaller granule size. The Hausner's index of the runs is summarized in Table 4. The Hausner's index was highly correlated with granule size (**Fig. 7**).

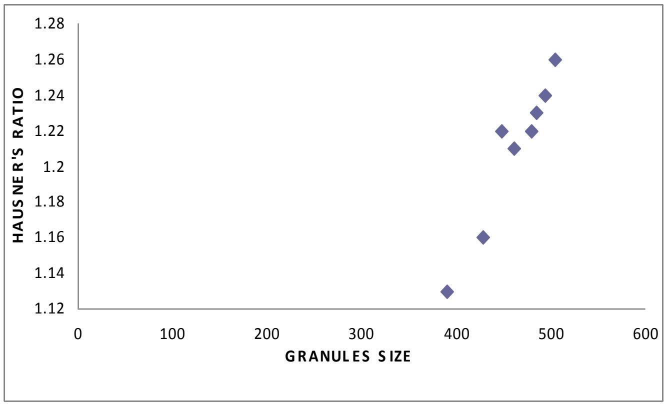

FIG. 7: THE OBSERVED GRANULES SIZE AS A FUNCTION OF THE OBSERVED HAUSNER INDEX

Hausner's indices lower than 1.26 was considered to be acceptable, because the granules are then considered to be free-flowing. Except for run B_2, all the runs resulted in acceptable Hausner's indices, which mean that granule sizes between 402 and 500 µm will probably result in an acceptable Hausner's index.

Angle of repose: The angle of repose (AOR) is used to characterize the granule flow. Small granules tend to have high surface-to-mass ratio. The AOR of the runs are summarized in Table 4. Figure 8 confirms that the AOR increases when the granule size increases. Angles of repose for all batches were in range of 29 to 32, considered to be acceptable. All the runs complied with range of angle of repose (**Fig. 8**).

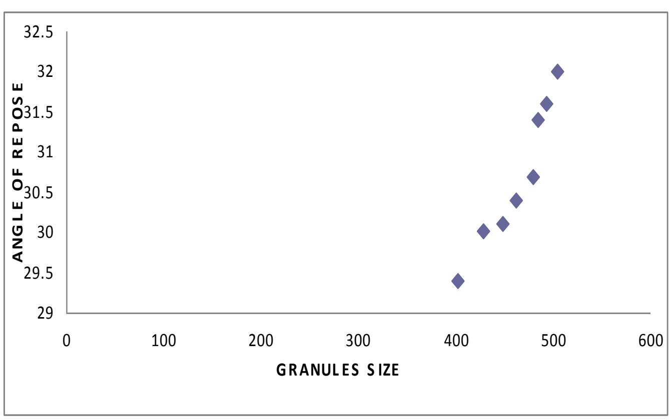

FIGURE 8: THE OBSERVED GRANULES SIZE AS A FUNCTION OF THE OBSERVED ANGLE OF REPOSE

CONCLUSION: This study shows that experimental design was an appropriate method to optimize the granulation process on the medium scale. It was shown in this study that granule size of the granulation could be optimized empirically, by considering the process variables. Optimal granules were obtained at low levels of the spray rate and high levels of the inlet air temperature. However, the granule size is the result of the balance between granule growth affected by the powder bed moisture content and the droplet size and the deformation force affected by the airflow rate. Optimal granule size and physical properties found at optimal variable settings of FBG.

This study investigated the influence of process variables and binder solution on the granulation process with special attention to the relationship between wetting and the granule growth profile. The growth mechanism depended on the interrelated contribution of the binder added and bed moisture content. The amount of binder added via solution mainly controlled the nucleation and the growth process, while the moisture content level was important in reducing the breakage and attrition during both the granulation phase and the drying phase. It is believed that the granulation process is almost controlled by the amount of binder added. Atomization air pressure also affects the granule breakage and flow properties of granules.

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