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Comparative analysis of granulation equipment and their influence on granule properties

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ABSTRACT:

Plain granules were manufactured without drug by using the granulation equipments like high-shear mixture granulator and fluid bed granulator. Various parameters such as size, shape, density and a variety of different flowability measurements were used to compare the granules. This comparison depicted that granule formation was dissimilar for both the equipments. The high-shear mixer granulation requires short process time and demonstrated better overall flow properties as compared to the fluid bed granulator. The granules formed after using high-shear granulator were denser as compared to the granules formed from fluid bed granulator which were less dense. Even though the make-up of the granules was the similar for high-shear mixture granulator and fluid bed granulator, the properties of the granules were dissimilar, resulting in differences in flow characteristics. The granules formed by high-shear mixture granulator are large & spherical in shape with low porosity, high bulk/tapped density, wide range of particle size distribution, whereas the granules formed by fluid bed granulator with Standard distribution plate are small in size, irregular in shape, have lower value of bulk/tapped density, narrow particle size distribution and high porosity. It was observed that both Carr's index and Hausner's ratio were satisfactory for high-shear mixture granulator, whereas they were only acceptable for Fluid bed granulator.

The varying mechanisms of granule growth have significantly affected both the particle size distribution and structure of the granules, depending on the equipment used. Evaluation of granule parameters concluded that the high-shear granules demonstrate superior flow characteristics than granules produced by the fluid bed granulator.

Key Words: Powder flow, fluidized-bed granulation, particle size, high-shear mixture granulation, density

INTRODUCTION

Powder flow is key requirement for pharmaceutical manufacturing process and depends on many factors of which granulation being one of the most important and critical factor. Granulation is a procedure during which the drug and excipients are mixed together by adding binding agents to form larger particles called granules[1]. Granulation process renders the material free flowing & enhances the consistency of drug distribution throughout the product. It also improves the appearance of the tablet & prevents the segregation of powder material in mixture. The process improves compaction characteristics of the powder which helps in formulation of tablets. Granulation is a crucial process that involves various challenges, including achieving size uniformity and managing physicochemical properties such as size of the granule, bulk density/tapped density, porosity, granule hardness, moisture content of granules, and compressibility, as well as ensuring the drug's physical and chemical stability[2]. The powder has the tendency to absorb moisture from atmosphere and may adhere and form cake. Whereas after granulation, granules absorb some amount of moisture and retain their flowability because of their size, thus granulation plays a very significant role in product quality & efficacy.

There are many types of equipment used for carrying out wet granulation where High Shear Mixture Granulator (HSMG) & Fluidized bed granulator (FBG) are commonly used in many pharmaceutical companies. In FBG, all steps from granulation to drying are carried out within the same equipment. On the other hand, in HSG, after granulation, the granules typically need to be dried either by vacuum or microwave drying within the granulator itself, or more commonly, by transferring them to a FBG for drying[3]. The fluidized granulator method thus saves wage expense, transfer losses, and duration and can be fully automated once all factors affecting granulation are optimized. However, a fluidized bed granulator (FBG) is costly, and optimizing both process and product parameters is crucial, necessitating extensive developmental work during the initial stages of scale-up and production. In contrast, high-shear granulation involves less developmental work because of the fewer operational parameters and limited interactions.[4,5].
In the current article an attempt is made to compare formulation and evaluation of granules by using HSG and FBG.

MATERIALS AND METHODS:

Lactose, Microcrystalline Cellulose (MCC), Sodium Croscarmellose, maize starch and HPMC E5 were received from Ganson Pvt Ltd to make the placebo formulation. All materials were passed through standard US no. 20 mesh sieves. Equipments used were Gansons Jacketed High Shear Mixer Granulator (2.5 kg) and Gansons Fluidized Bed Granulator (10 kg) with Standard Air Distribution Plate

FORMULATION OF GRANULES:

Preparation of Binder Solution & Powder Blend

An HPMC solution was created by dispersing 50 g of HPMC powder (Grade E5) into 200 ml of distilled water and continuously stirring with a mechanical stirrer at room temperature until a homogeneous solution was achieved. Product intermediates for tablet preparation were obtained after accurately measuring the final quantities and then the batches were mechanically mixed in High Shear Mixture Granulator (Batch A) & Fluidized Bed Granulator (Batch B) for 10 minutes to ensure proper mixing. The model formulations consisted of Lactose (16%), MCC (54%), Sodium Croscarmellose (10%), Maize Starch (20%) & HPMC (12.5%).

The wet granulation formulations were prepared in HSMG & FBG where the materials that were to be granulated were first dried, mixed, and then the binding solution was added during mixing and subsequently the wet mass formed was wet sieved, dried and sieved again to control agglomerate growth.

EVALUATION OF GRANULES:

Moisture content[6,7]

The moisture content of the granules was measured by determining the loss on drying at 105°C using a Mettler Toledo HG63 halogen moisture analyzer. Twice samples of 5.0 g were evaluated.

The final loss of weight is calculated by,

Percent Moisture content = Moisture Loss (g))/ Initial Sample weight (g) ×100

Moisture Loss= Initial weight of sample (g) – Final weight of sample (g),

Initial weight of sample = Weight of sample before drying

Final weight of sample = Weight of sample after drying

Sieve Analysis[6,7]

Sieve analysis evaluates the PSD of granular materials by passing the material through a series of sieves with progressively smaller mesh sizes and measuring the quantity of material retained by each sieve as a proportion of the total mass. By using the mechanical shaker the procedure was carried out in 2 phases for 20 minutes each at high speed.

% Retained = (Weight Retained on Mesh (in grams)) / (Total weight Sieved (in grams))

Angle of repose[6,7]

The angle of repose is the angle between the horizontal base of the bench surface and the edge of a conical pile of granules. Once the cone of the sample is formed, the height (h) of the cone and the radius (r) of its base need to be measured.

The angle of repose *(θ)* is calculated by using the formula

$$\text{Angle of Repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right)$$

Bulk and Tapped Density[6,7]

Bulk and tapped densities were measured following USP methods. The bulk volume is determined by tapping the cylinder twice manually on a flat table surface.

Bulk Density of granules (ρb) =Weight of powder/Volume of powder

Tapped Density (ρt) = Weight of powder / Tapped volume of powder

Compressibility Index and Hausner's Ratio [8,9]

The bulk density and tapped density of granules are used to calculate Carr's compressibility index (CI) and Hausner's ratio (HR), which assess the flow characteristics and powder compressibility.

Compressibility Index = 100 ×(tapped density- bulk density)/(tapped density)

Hausner's Ratio = Tapped density/bulk density

Result & Discussion:

The size & shape of particles play a very significant role in compression of a tablet. If the particles are spherical they have less resistance to flow. The large size particles have wide size distribution whereas smaller particles have narrow size distribution. Smaller particles have good porosity than the larger ones[10,11]. Therefore for better compression particles should be large & spherical.

PSD (PSD) of granular material is a mathematical function that describes the relative amount, usually by mass, of particles present based on their size. Granules with a diameter ranging from 150 to 600 μm, a spherical shape, and uniform formulation components are deemed optimal. Particles with diameters under 150 μm are classified as fines, while those exceeding 600 μm in diameter are considered oversized.

Table1: Results of PSD for HSMG and Fluid bed granulator

Mesh Size	% Retained	
	HSMG	FLUID BED GRANULATOR Std. plate
10	2.63	0.45
20	5.44	2.07
44	47.7	21.4
52	26.82	16.59
85	91.52	18.62
100	36.9	17.16
200	64.98	12.15
Not Retained on 200	60.53	17.9

PSD has effect on the flowability which increases with particle size. Increasing the particle size decreases the bulk density and a wide PSD will lead to lower viscosity thus increasing flowability. In the present study the large agglomerates were observed for the high shear granulation contributing to its wide PSD and reverse was observed for FBG showing particles with narrow size distribution. The reason for different size distribution can be because of differences in granulation process including liquid spray rate of binder and processing time.

Table 2: Loss on Drying

Sr. No.	LOD
HSMG	5.85%
FLUID BED GRANULATOR Std. Plate	4.56%

When the moisture content was low in granules, the size distributions for both the equipments was found to be narrow. On the other hand, at high moisture level, the oversized agglomerates were formed by high shear granulation while the PSD for the FBG would not change significantly as even though the larger agglomerates are formed they would be breakable and irregular in shape with high porosity and consequently will break down during attrition and mixing[10,11].

Table 3: Powder Characteristics

MACHINES	POWDER CHARACTERISTIC					
	Mean Size	Size Distribution	Granules Shape	Granules Porosity	Bulk/Tapped Density	Flowability
HSMG	Large	Wide	Spherical	Low	High	Good
Fluid bed granulator std.	Small	Narrow	Irregular	High	Low	Poor

The table 3 results depicted that the granules formed by HSMG are large & spherical in shape. Besides the granules had low porosity, high bulk/tapped density & range of size distribution is wide, whereas granules formed by FBG are small in size, irregular in shape, have lower value of bulk/tapped density, narrow PSD and high porosity in comparison to HSMG.

In the context of fluidized-bed granulations the formation of granules progresses slowly and steadily through the coalescence of nuclei followed by formation of small size of granules as the binder was sprayed continuously onto the bed. With low shear forces in FBG, the granules formed are irregular in shape and are highly porous.

Table 4. Comparative Evaluation Parameters of granules

	HSMG	Fluid bed granulator with Std. Plate
Bulk Density	0.314	0.1956
Tapped Density	0.351	0.2477
Angle of Repose	23.96	33.81
Carr's Index	10.39	21.03
Hausner's Ratio	1.116	1.266

High bulk/tapped density shows Good Flowability. The bulk density for HSMG is 0.3142, for Fluid bed granulator (Std.) is 0.1956. The tap density for HSMG is 0.3507, for Fluid bed granulator (Std.) is 0.2477 thus indicating HSMG shows good flow.

The assessment of flow properties of the granules are dependent on critical factors like size, shape, particle size distribution and density of granules. The flowability of the granules are important to manufacture the tablet with particular properties. Both compressibility and flowability are indicated by the Carr index and Hausner's ratio. A Carr index below 15 indicates low compressibility and good flow properties, while a value above 25 suggests a highly compressible powder with poor flow characteristics.

The Carr's index for HSMG was calculated to be 10.39 and for FBG (Std.) to be 21.03 similarly the Hausner's Ratio for HSMG was calculated to be 1.116; for FBG (Std.) to be 1.266 as per the table no. 4. As per the standards we can say that the Carr's Index and Hausner's Ratio for HSMG was good [12,13], for FBG (Std.) was passable. Thus result of Carr's index and Hausner's Ratio ensures excellent compressibility and flowability. The elevated Carr index for fluidized-bed granulations indicates porous granules that are likely to be compressible. However, these granules, being of lighter density and irregular shape, may experience flow challenges. The variation in the Carr index across fluidized-bed granulation trials reflects differences in particle size distribution, with larger granules—exhibiting better flow properties—being produced at lower fluidization velocities.

The static angle of repose also serves as an indicator of flowability. The angle of repose for HSMG was calculated to be 23.963 and for FBG (Std.) was 33.81 (Table 4). As per the standards we can say that the angle of repose of HSMG was excellent and for Fluid bed granulator (Std) was good. Thus both types of granulators decreased the angle of repose and thus ensures excellent flowability[14,15]. The measurement of angle of repose alone is not adequate to identify minute changes in flowability.

The size & shape play a very important role in compression of a tablet. If the particles are spherical, they have less resistance to flow. Also, the large size particles have wide range of size distribution whereas small particles have narrow range of size distribution with good porosity than the large ones[16,17,18]. Therefore, for better compression particles should be large & spherical in combination with few fines which can be used to fill the gaps between large particles [19,20].

Conclusion

The present research study concluded that wet granulation of powders can be effectively performed in HSMG and FBG. In these equipments it was essential to select appropriate operating conditions for the manufacturing of desired granules by wet granulation. In HSMG the machine parameters like impeller speed, jacket temperature & kneading time are important whereas in FBG; temperature, flow rate of fluidizing air & temperature of product is important. Due to the varying mechanisms of granule growth, the use of different equipment has significantly influenced the particle size distribution (PSD) and structure of the granules, as evident in the results. The evaluation of granule parameters led to the overall conclusion that high-shear granules demonstrate better flow properties compared to those produced by a fluidized bed granulator.

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