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Comparison of Different Granulation Techniques for Lactose Monohydrate

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ABSTRACT
The objective of this study was directed to improve the physical and technical properties of poorly flowing and highly cohesive Lactose monohydrate to solve the most important problem that affects tablet manufacture. To overcome all the problems related to lactose granulation is required. Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms. Granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amounts of fine particles. The results will be improved yields, reduced tablet defects, increased productivity. Pharmaceutical products are processed all over the world using the direct-compressing, wet-granulation, or dry granulation methods. Which method is chosen depends on the ingredients individual characteristics and ability to properly flow, compresses, eject, and disintegrate. Then the proper granulation process can be applied. The objective of present article was to focus on the best possible granulation technology that gives good results based on evaluation of different granule properties, namely the Carr's index, Hausner's index, Angle of repose, were evaluated for granule prepared by different binders and different techniques. Finally, the tabletting process showed low values of ejection forces, good tablet properties (weight uniformity, hardness, friability, and disintegration) indicating good compressibility of the prepared granules using Fluidized Bed Processor (HPMC 2.5% as binder) and Coprocessing of Lactose.

Keywords: Lactose monohydrate, Granulation process, Different techniques, Fluidized bed Processor, Coprocessing.

INTRODUCTION

Lactose is one of the most frequently used fillers. Available in different forms depending upon the crystallization conditions and in various grades with different particle sizes and different compaction properties. [1-2] Lactose is Directly Compressible (DC) adjuvant so DC also has some disadvantages: More required excipients and flowability, segregation of blend, sensitivity for lubricants, lamination and capping behavior. [3] Granulation is used mainly to improve flow and compressibility of powders and to prevent segregation of the blend components. Particle size of the granulate is mainly affected by the quantity and feeding rate of granulating liquid. [4] Most of literature gives idea about the flow characteristic improvement by different approach. [5-9] The objective of this study was hence to evaluate the effect of different granulation techniques of Lactose Monohydrate: Evaluate the binder bridges which can form in matrix granules prepared with different granulation technique and different matrix forming agent. [10-11] Evaluate the physical property of lactose granules prepared by different granulation techniques; and to improve the granulation efficiency and the final granule characteristics for the Lactose monohydrate that is to be granulated via different granulation techniques. To evaluate the effect of different granulation techniques on tablet strength. [12]

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MATERIALS AND METHOD

Lactose Monohydrate obtained from Fischer Scientific Lot No.5556 6901-1, HPMC obtained from S d fine Chem. Ltd. Batch No.1092/0209/1808/13, Starch Corn (Maize LR) obtained from S D fine Chem. Ltd. Batch No. F102/1110/2205/13, PEG obtained from Fischer Scientific Lot No.8959 6712-1, PVP K30 obtained from Central Drug House Lab. Lot No. 01105, and Isopropyl Alcohol obtained from Fischer Scientific Lot No.7547 6803-2.

Experimental matrix

The experimental test matrix was set up in order to study effect of different binders in different concentration on flow property of poorly flowable Lactose Monohydrate using different granulation techniques, followed by evaluation of tablet properties.

Different techniques for preparation of lactose granules

Granules of lactose were prepared using:

- Sieving technique,
- Co-processing of lactose and
- Fluid bed granulation technique

Sieving Method [10]

In this wet granulation method wet mass of Lactose using binder solution was prepared. Then sifting of wet mass from sieve done by manually. Followed by drying in oven at 60°C. Then screening for uniform granules and for breaking of lumps by passing it through higher sieve size. This method mostly used in academic lab for preparation of granules manually.

Co processing of Lactose [7, 13]

Material science plays a significant role in altering the Physicomechanical characteristics of a material, especially with regard to its compression and flow behavior. Coprocessing excipients offers an interesting tool to alter these Physicomechanical properties [15]. The General procedure for preparation of Co processed Lactose is give below:

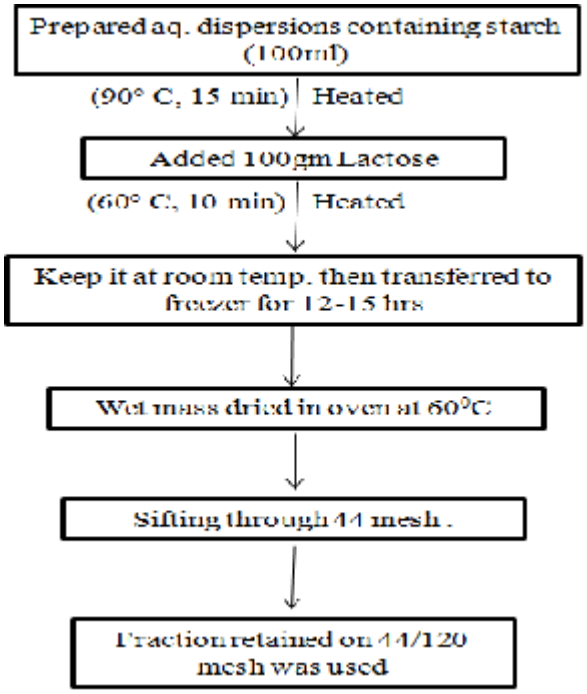


Fig. 1: Preparation of Coprocessed Lactose

Fluid bed granulation technique [5, 8]

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. Afterwards the aqueous solution of a binder (2.5% HPMC) 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. The finalized process variables are described in following Table:

Table 1: List of Process Variables for FBP

Process Variables	Value
Peristaltic Pump Flow Rate	1.77 RPM
Batch Size (gm)	250 gm
Inlet Air Temperature (°C)	65°C
Binder Atomizing Pressure (kg/cm^2)	0.011
Fluidization Pressure (kg/cm^2)	0.08

Micromeritic evaluation of Lactose Granules [14]

Final granule size distribution: Using sieve shaker and a set of sieves (40, 60, 70, 80, 100, 120, 140, 170 Mesh size), a 50 g of the final product was shaken for 10 min to obtain the size distribution.

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:

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

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

Where, ρ1 & ρ2 are the apparent and tapped densities of the material, vb & vt are the bulk and tapped volumes of the material and ρt & ρb are the tapped and bulk density of the material respectively.

Angle of repose: Angle of repose has been used to characterize the flow property of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. The angle of repose is the constant, three dimensional angle assumed by a cone like pile of material formed by these method. The height of the funnel through which powder passes may be fixed relative to the base or the height may be varied as the pile forms.

$$\tan(\alpha) = \frac{\text{height}}{0.5 \text{ base}}$$

Where, α is Angle of repose

Microscopy (Using Motic Microscope): Used for evaluation of surface morphology and granule shape and size to check the effect of this on flow characteristics as well tablet strength.

Tablet Properties [12]

Tablet was prepared by direct compression. Then evaluated the effect of different granulation techniques on tablet properties following different parameters done:

Average weight of tablets: Twenty tablets were dedusted and weighed accurately on digital weighing balance. Average weight of tablets was calculated using following formula:

Average weight of tablets = Weight of 20 tablets /20

Hardness: Hardness of the tablets was measured using Monsanto hardness tester. The hardness was measured in Kg/cm^2 for tablets of each batch.

Friability test:

Apparatus: Roche Friabilator

Procedure: Weighed 20 Tablets (X) were added to the friability test apparatus which was already set to 25 rpm. After completion of 4 minutes, tablets were removed; dedusted it and weight of the tablets were noted down (Y).

Friability calculated by following formula:

$$\% \text{ Friability} = X\text{-}Y/X * 100$$

Acceptance criteria: Friability of tablets should be less than 1%.

Table 2: Flow Property Characteristics for Prepared Granules

Binder	Bulk Density	Tapped Density	Hausner's Ratio	% Compressibility Index	Angle of Repose (Ø)
Lactose As Such	0.51	0.69	1.35 (Poor)	25.97 (Poor)	Ø=47.35 (Poor)
Ethanol	0.48	0.61	1.27 (Passable)	21.32 (Passable)	Ø=37.48 (Fair)
5% PEG 4000	0.49	0.57	1.16 (Good)	14.03(Good)	Ø=13.81 (Excellent)
2.5%PEG 400	0.45	0.54	1.20 (Fair)	16.67 (Fair)	Ø=16.55 (Excellent)
5% PEG 400	0.43	0.53	1.23 (Fair)	18.86 (Fair)	Ø=16.67 (Excellent)
2.5%HPMC 15cps	0.41	0.52	1.27 (Passable)	21.15 (Passable)	Ø=16.85 (Excellent)
5% HPMC 15 cps	0.45	0.55	1.22 (Fair)	18.18(Fair)	Ø=16.21 (Excellent)
2.5% PVP k30	0.40	0.47	1.18 (Good)	14.89 (Good)	Ø=17.61 (Excellent)
5.0% PVP k30	0.42	0.50	1.19 (Fair)	16.0 (Fair)	Ø=15.55 (Excellent)
Co processed Lactose 45# Sieve	0.49	0.53	1.08 (Excellent)	7.55 (Excellent)	Ø=14.995 (Excellent)
Co processed Lactose 70# Sieve	0.21	0.24	1.14 (Good)	12.5 (Good)	Ø=12.09 (Excellent)
Co processed Lactose using Anti solvent	0.47	0.53	1.13 (Good)	11.32 (Good)	Ø=15.26 (Excellent)
FBP (1.25% HPMC)	0.37	0.41	1.12 (Good)	9.7 (Excellent)	Ø=14.62 (Excellent)
FBP (2.5% HPMC)	0.39	0.43	1.10 (Excellent)	9.3 (Excellent)	Ø=14.34 (Excellent)

Disintegration test:

Apparatus: Disintegration test apparatus

Media: Distilled water

Procedure**:** The assembly was suspended in the specified liquid medium in a 1000 ml beaker. The volume of liquid was taken such that when the assembly was in highest position the wire mesh was at least 25 mm below the surface of the liquid and when the Assembly was in lowest position the wire mesh was at least 25 mm above the bottom of the beaker. One tablet was placed into each of the tube of the assembly and disk was added to each tube. The apparatus was operated for specified time and temperature at 37±2°C. Time for complete disintegration of tablet was note down.

Acceptance criteria: The tablets pass the test if all of them have disintegrated.

RESULTS AND DISCUSSION

Effect of Binder

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 and ultimately affected on powder flow property. Different binder and there flow property evaluated but the only HPMC 5 CPS at 2.5% shows good flow property at low concentration compared to other binders. So 2.5% HPMC 5CPS used as optimized binder for fluidized bed granulation.

Effect of Different Granulation Techniques on Final Granules Flow Property Characteristic

Carr's Index: The Carr's index value provided some indication of the flow of behaviour 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 2 showed no major difference in the values of angle of repose and Carr's index. Coprocessed Lactose and FBP granules (2.5% HPMC) showed the lower value angle of repose and Carr's index, resulting in better flow compare to other batches.

Hausner's Ratio: The Hausner's Ratio 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. Hausner's indices lower than 1.16 was considered to be acceptable, because the granules are then considered to be free-flowing.

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 2. Angles of repose for all batches were in range of 12 to 18, considered to be acceptable.

Particle size of the granules: From the particle size determination of granules by sieve method it was concluded that FBP granules showed maximum retention of granules on # 40 and Co processed lactose showed maximum retention of granules on # 60 in comparison with other batches. Hence, FBP and co processed lactose showed the maximum uniformity in granule size.

Table 3: Particle Size Distribution Study for Prepared Granules

Sieve No.	% Wt. retained of granules			
	Lactose as such	Co processed Lactose Batch 1(45 # Sieve)	Co processed Lactose Batch 2 (70 # Sieve)	FBP granules using 2.5% HPMC
40	6.92	34.35	-	58.6
60	16.71	44.56	-	35.6
70	20.90	10.46	-	3.13
100	2.58	6.16	18.22	-
120	-	2.76	23.64	1.24
140	-	-	9.22	-
170	-	-	17.74	-
Fines	52.79	1.67	31.12	1.5
Loss	0.09	0.04	0.06	0.03
Particle size range	88-250 micron	149-420 micron	88-149 micron	250-420 micron

Effect on Tablet Property: From the evaluation of tablet property like Wt. variation, Hardness, % Friability, Disintegration test it was concluded that tablet prepared using co processed lactose shows higher disintegration time and low friability with acceptable hardness then that of Lactose as such tablet. On other side tablet using FBP granules shows optimum disintegration time with that of friability and hardness. Hence, Tablets prepared using co processed lactose and FBP granules shows good results compared to others batches.

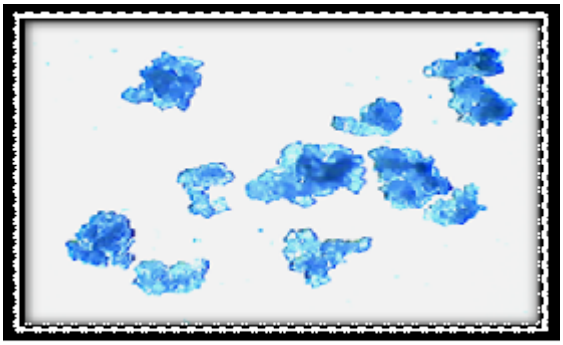
Table 4: Evaluation of Tablet Prepared Using Different Granules

Lactose Granules	Mean wt. of Tablet (mg)	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (sec.)
Lactose As such	502.65	6.5	0.78	45 sec
Coprocessed Lactose 70 # Sieve	507.6	7	0.39	90 sec
Coprocessed Lactose 45# Sieve	499.8	7.5	0.58	240 sec
FBP Granules (2.5%HPMC)	501.5	6	0.49	150 sec

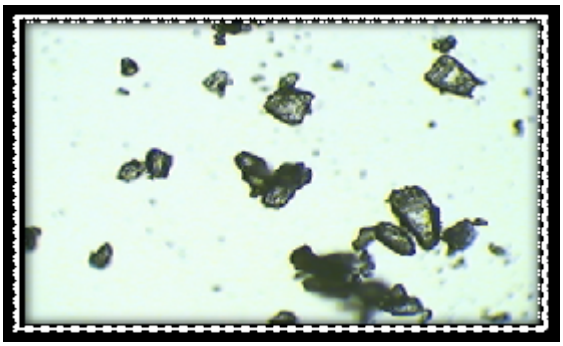
Microscopic analysis of different granules: The microscopic analysis (using Motic Microscope) of different

granules shows that Coprocessed lactose (45#) having clustered like appearance where as Coprocessed lactose (70#) shows rod crystal. On other side Lactose granules using FBP shows uniform granules with less void on granule surface.

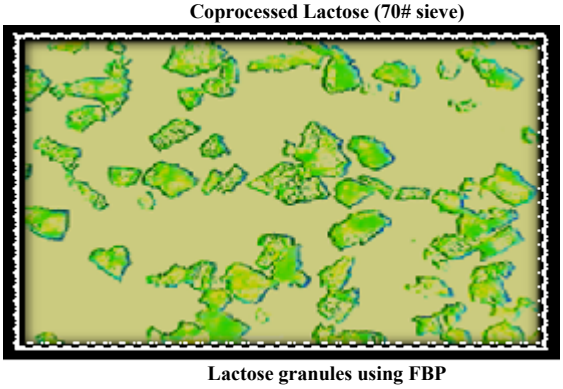
Lactose as such



Coprocessed Lactose (45# sieve)



Coprocessed Lactose (70# sieve)



Lactose granules using FBP

Fig. 2: Microscopy of Different Granules for Lactose Monohydrate

In conclusion, the findings of this work showed that granulation could be an interesting method to improve the flow property of a poorly flowable Lactose Monohydrate, when associated with a suitable binder and granulation technique. Direct study of the composition of every individual binder bridge formed from soluble materials in the granules is impossible, but their indirect evaluation done by evaluation of tablet property. These data provide additional information towards an understanding of granule formation in a small-scale in academic lab.

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