ORIGINAL ARTICLE

Application of a convenient and cost-effective granulation technology for the formulation of tablets using conventional excipients

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In the present investigation, suitability of a cost-effective and convenient granulation technique that is, moisture activated dry granulation (MADG) process for high drug loading in tablet formulation was studied. In this work, effect of the amount of water on flow properties of granules as well as an effect of mixing time on surface morphology of granules was studied. Paracetamol (PCM) immediate release granules were prepared using conventional excipients such as polyvinylpyrrolidone K-30, Kollidon VA 64 (as binders), and simple equipments by MADG technique. The prepared granules were evaluated for flow properties and tablets were compressed using optimized granule formulation. The prepared granules possessed good flow properties that is, angle of repose was 32.11 and percent compressibility index was 19.44. Tablets disintegrated in 2.08 min and 89% of the drug was released within 30 min. All the results were comparable with PCM tablets prepared by wet granulation method. Therefore, from the above studies it was concluded that MADG process may be effectively adopted by using Kollidon VA 64 as a binder in tablet formulations where high drug loading is to be achieved, where all the parameters of the formulation can be obtained within specified limits using this simple, convenient, less time consuming, economical, and efficient method of granulation.

Key words: *Moisture activated dry granulation, paracetamol, precompression parameters and postcompression parameters, wet granulation process*

INTRODUCTION

Among all dosage forms, tablet is the most popular dosage form. About half of all prescriptions are dispensed in compressed tablets. Since many years a comprehensive research is being done to study processes used to manufacture tablets. Efforts have been made to simplify processes, reduce processing time, increase efficiency, and improve drug content uniformity. Traditional or conventional granulation processes include high shear granulation, fluid-bed granulation, continuous granulation, and roller compaction.[1-2] All of these processes are excellent ways to produce quality granules for tableting or capsule filling, but they require significant production time and energy. Ullah *et al*. in 1987 described a modified wet granulation process that was named as moisture activated dry granulation (MADG).[3] MADG is a process where granules are formed by moisture and heat is not used for drying of granules. During this process, the generation of moist agglomerates is followed by the stepwise addition and blending of common pharmaceutical ingredients that absorb and distribute the moisture, which results in a uniform, free-flowing and compactable granulation. In MADG process, the whole process is considerably shorter than a typical wet granulation.

This technique is advantageous as it is simple, processing time is short, drying and milling steps are excluded, and energy is required. In spite of several advantages associated with MADG very few pharmaceutical manufacturing companies are adopting this as a method of granulation for compression of tablets. Reasons of nonpopularity associated with MADG are the requirement of costly functional excipients and special equipments required for this process.[4] This technique has been used for the development of tablet formulations by few researchers,

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but maximum achieved drug loading is only 60-65%.[5-7] Thus, it is further required to establish the usefulness of this process for still higher drug loading to prove its versatility.

Therefore, the present work is aimed at establishing MADG technique using conventional excipients and simple equipments for the preparation of tablet formulations with high drug loading. Paracetamol (PCM) was selected as a model drug for these studies because of its higher dose and low aqueous solubility. Effect of type and amount of binder, amount of moisture and mixing time on the pre- and post-compression parameters was studied. Tablets were prepared by MADG process and parameters were compared with that of tablets prepared by wet granulation process.

MATERIALS AND METHODS

Materials

Paracetamol was purchased from Granules India Ltd., Hyderabad, India; polyvinylpyrrolidone (PVP) K-30 from New Arihant Chemicals, Mumbai, India; Kollidon VA 64 from BASF, Mumbai, India; colloidal anhydrous silica from Evonik Industries, Mumbai; Microcrystalline Cellulose from FMC Biopolymer, Bengaluru, India; Sodium Starch Glycolate from Ascot Pharmachem Pvt. Ltd., Gujarat, India; Talcum from Neelkanth Minechem, Rajasthan, India and magnesium stearate was purchased from Nitika Chemicals, Nagpur, India. All other reagents and solvents were of analytical grade.

Methods

Preparation of tablets by moisture activated dry granulation

Moisture addition stage

Blends of PCM along with varying compositions of PVP K-30 and Kollidon VA 64 were prepared as per compositions given in Table 1 using planetary mixer (Marvold PD-250) fixed with a spray gun. A fixed quantity of water was sprayed on to powder bed, while being mixed. After addition of water, stirring was continued for 10 min and blends were processed for the next stage.

Moisture absorption stage

To the blends of the first stage, Microcrystalline Cellulose (Avicel PH 102) and colloidal anhydrous silica were added as moisture absorbents and mixing was continued. After mixing for 5 min, sodium starch glycolate was added and blending was continued further for 5 min. Then, while mixing, magnesium stearate was added and blended for sufficient time to achieve adequate lubricity. Resulting granules were then evaluated for precompression parameters and were compressed using compression machine (Accura press, Fluid pack, D tooling). Tablets were then evaluated for postcompression parameters such as hardness, friability, thickness, weight variation, disintegration, and dissolution.

Effect of the amount of water on flow properties and particle size of granules was studied. For this, optimized formulation batch from the earlier studies was selected and quantity of water was varied from 2% to 8%. Composition of these formulations is given in Table 2. These blends after mixing for 10 min were then evaluated for flow properties and particle size analysis.

Optimized batch obtained was then studied for influence of mixing time on the flow properties by increasing mixing time during moisture addition stage from 10 to 30 min. These blends were then evaluated for change in the particle shape, size, and morphology using scanning electron microscopy. Table 3 gives composition and formulation codes of batches so prepared.

Table 1: Composition of paracetamol tablet by moisture activated dry granulation process

Formulation Code	Ingredients	Formulation Codes (Quantities in percentage)				
		F1	F2	F3	F4	F5
1.	PCM	83	83	83	83	83
2.	PVP K 30	8	6	4	2	0
3.	Kollidon VA 64	0	2	4	6	8
4.	Water	2	2	2	2	2
5.	Colloidal anhydrous silica	0.6	0.6	0.6	0.6	0.6
6.	Microcrystalline cellulose PH 102	3	3	3	3	3
7.	Sodium starch glycolate	1.9	1.9	1.9	1.9	1.9
8.	Purified talc	1	1	1	1	1
9.	Magnesium Stearate	0.5	0.5	0.5	0.5	0.5

Table 2: Composition of formulations prepared to study the effect of the amount of water on Paracetamol granules prepared by moisture activated dry granulation technique

Ingredients	Formulation Codes (Quantities in percentage)			
	F3A	F3B	F3C	F3D
Paracetamol	86.3	88.2	90.08	91.98
PVP K30	2.85	2.9	2.96	3.01
Kollidone VA64	2.85	2.9	2.96	3.01
Water	8	6	4	2
Water droplet size	1 to 2 mm	1 to 2 mm	1 to 2 mm	1 to 2 mm

Table 3: Composition of formulations prepared to study the effect of mixing time on Paracetamol granules prepared by moisture activated dry granulation technique

Ingredients	Formulation Codes (Quantities in percentage)		
	F3AM1	F3AM2	F3AM3
Paracetamol	86.3	86.3	86.3
PVP K30	2.85	2.85	2.85
Kollidone VA64	2.85	2.85	2.85
Water	8	8	8
Mixing time	10	20	30

Batch size in all the cases was 5 kg. For comparison granulation was also carried out using conventional wet granulation process and tablets were compressed. Formulation code was given as FWG and the batch was evaluated for pre- and post-compression parameters.

Scale up studies was carried out by increasing batch size from 5 to 50 kg. Whole granulation process was carried out in rapid mixer granulator fitted with a spray gun (Jaguar, 561/2003; China) and the resulting granules were compressed using 27 station compression machine (CMB4, Fluid pack, India, D tooling) The batches were then evaluated for the selected pre- and post-compression parameters.

Evaluation of granules

Precompression parameters

Bulk and tapped density

Both bulk density (BD) and tapped density (TD) of the blends/granules were determined using (ETD 1020, Electro Laboratory, Mumbai, India). A quantity of 20 g of powder from each formula was poured into a 100 ml measuring cylinder. After observing the initial volume, the cylinder was allowed to fall under its own weight on a hard surface from the height of 2.5 cm at 2 s intervals. The tapping was continued until no further change in volume was noted. BD and TD were calculated using the following formulas:

BD = Weight of the powder/volume of the packing

TD = Weight of the powder/tapped volume of the packing.

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index

Carr's index (%) = ([TBD − LBD] ×100)/TBD

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The blend/granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$\tan \theta = h/r$

Where h and r are the height and radius of the powder cone, respectively.

Loss on drying

Loss on drying of the granules for each batch was determined using a moisture balance (Mettler PM 480, Switzerland) fitted with an infrared heating unit (Mettler LP 16).

Determination of the mean particle size

Sieve analysis was carried out using mechanical sieve shaker (Erweka Co., Frankfort, Germany) containing a series of US standard sieves, ranging in size from #30 to #170 mesh. Accurately weighed 25 g of granules were placed on the top sieve and mechanically shaken for 10 min. The fraction retained on each screen was determined, and the geometric mean diameters of the granules were calculated from the sieve analysis data.

Postcompression parameters

Hardness and friability

For each formulation, the hardness and friability of six tablets were determined using the Monsanto Hardness Tester (Cad Mach, Ahmadabad, India) and the Electro Laboratory Friabilator (Electro Laboratory, EF - 1W, Mumbai, India), respectively.

Thickness

The thickness of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were evaluated, and average values were calculated.

Weight variation

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Contech Instruments Ltd., Navi Mumbai, CA 223, India), and the test was performed according to the official method as per Indian Pharmacopoeia.

Disintegration time

The disintegration test on tablets prepared by MADG was carried out to compare the values obtained with that of tablets prepared by wet granulation method that is, whether DT of tablets falls within the specifications or not, when this novel granulation technique was adopted. The disintegration test was performed in the USP disintegration apparatus (Electro Laboratory, Mumbai, India). Distilled water was placed in the tubes of the container. The time required by tablets to disintegrate completely was noted as disintegration time (DT). The average *in vitro* DT of six tablets from each formulation was noted and reported as mean ± standard deviation.

Content uniformity

For evaluation of content uniformity, 10 tablets were weighed individually. Each single tablet of PCM was added to 50 ml of 0.1 M sodium hydroxide, then diluted with 100 ml of water, and was shaken for 15 min. Then sufficient water was added to produce 200 ml solution which was then mixed and filtered. 10 ml of the filtrate was diluted to 100 ml with water and 10 ml of this solution was added to 10 ml of 0.1 M sodium hydroxide, further diluted to 100 ml with water. Absorbance of the resulting solution was measured at the λmax 257 nm (Shimadzu, UV2401PC, Japan).

Dissolution studies

Dissolution studies were carried out using dissolution tester USP apparatus 2 (Paddle) (Electro Laboratory, TDT, 08 L, Mumbai, India). The dissolution medium consisted of 900 ml of phosphate buffer, pH 5.8 at 50 rpm for 30 min maintained at 37 ± 0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer (Shimadzu, UV2401PC, Japan), at λmax 257 nm. The release studies were conducted in triplicate (six tablets in each set), and the mean values were plotted versus time.

RESULTS AND DISCUSSION

The granules of different formulations were evaluated for the angle of repose, BD, TD, and compressibility index. Data related to flow properties of granules of different formulation batches obtained after 10 min mixing time is given in Table 4. BD and TD values for all the formulations prepared by MADG process ranged from 0.55 to 0.71. BD and TD values of batch prepared by wet granulation process were found to be 0.58 and 0.72, respectively. The results of angle of repose and compressibility index (%) ranged from 29.70 to 38.89 and 9.52 to 22.53, respectively. It was found that increasing the quantity of Kollidon VA 64 in the initial blend improved the flow properties. In fact, when Kollidon VA 64 is used alone then flow properties are not only excellent, but even better than granules prepared by wet granulation method. This finding suggests that Kollidon VA 64 is a better granulating agent for formulation of granules using MADG technique.

LOD for all formulations was found to be well below 2.50% [Table 4]. This indicated that change in the proportion of binding agent does not affect moisture holding capacity of blends.

Figure 1 shows particle size distribution of formulation batches from F1 to F5 and FWG. This analysis revealed that mean granule size obtained by MADG process is smaller than that obtained with wet granulation process. This is due to the lower quantity of moisture present as has been observed by earlier researchers.[4] Among the different batches prepared by MADG process it was seen that, increase in the quantity of Kollidon VA 64 increased particle size of granules. An excipient with greater binder capacity binds more strongly to more particles and thus larger particles were observed.[8] This observation confirms Kollidon VA 64 as better binding agent than PVP K-30. These results are consistent with results of flow properties given in Table 4. As the concentration of Kollidon VA 64 is increased flow properties of the granules improved.

Data of postcompression parameters of these batches of granules is given in Table 5. The thickness of the tablets ranged from 2.2 ± 0.3 mm. The average percentage deviation of 20 tablets of each formula was less than ±5%. The hardness and percentage friability of the tablet of all the batches ranged from 3 to 6 kg/cm^2 and 0.19-1.0%, respectively. Drug content was found to be uniform among different batches of the tablets and ranged from 100% to 90%. All the batches passed the DT test except batch no F5 that is, it was within the prescribed limit 15 min as compared with the formulation F5 which showed disintegration above 15 min. This may be attributed to the presence of PVP K-30 in all the other formulations. As it is reported to be a well-known binder as well as a better pore former.[9] As seen from Figure 2 formulation F5 showed only 35% drug dissolution within 30 min, while all other formulations showed more than 75% drug dissolution within 30 min. A clear trend was seen with the increased concentration of Kollidon VA 64 and retardation in release rate. From these findings it may be said that the presence of PVP K-30 is essential along with Kollidon VA 64 as a binder to get desirable dissolution profiles. Based on these

Table 4: Results of precompression parameters of moisture activated dry granulation granules

Parameters	F1	F2	F3	F4	F5
Bulk Density	0.55	0.55	0.56	0.58	0.57
Tapped Density	0.71	0.71	0.65	0.65	0.63
Comp. Index (%)	22.53	22.53	13.80	10.70	9.52
LOD	2.16	2.18	2.00	2.14	2.10
Angle of Repose	38.89	34.98	33.71	31.65	29.70

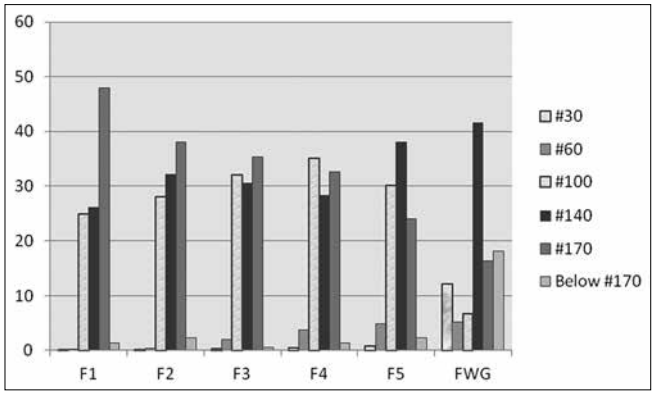

Figure 1: Effect of nature and quantity of binder on particle size distributions

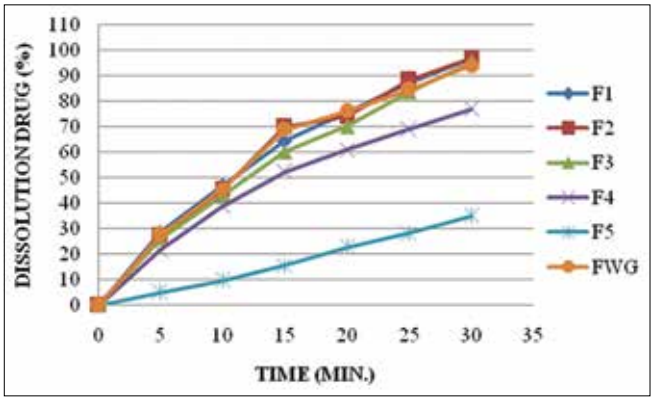

Figure 2: Dissolution profile of paracetamol tablets formulated using varying concentrations of binders

results, F3 formulation was selected for further studies as it was giving optimum results for all the parameters [Table 5].

Table 6 lists the flow properties of F3 formulation prepared by varying amount of water. It was noted that increasing the quantity of added moisture make the granules more flowable. This was due to the formation of more number of larger agglomerates that improves flow properties. Particle size analysis of these batches supported these findings [Figure 3]. At 2% added moisture granules retained on #12 were <10%, but with 8% this amount increased up to 26%. However, LOD values were for batch F3A and F3B were significantly more than 2%. Higher LOD value does not yield tablets with acceptable postcompression parameters and hence, the process is not recommended to be carried out using more than 4% of added moisture.

Scanning electron microscopy was performed to study the effect of mixing time on the morphology of particles. Figure 4 shows the scanning electron micrograph of initial blend of PCM and binders. A mixture of particles is seen with varying sizes and shapes. It is clearly visible that all the particles exist independently and this explains poor flow properties of this blend. Figure 5 shows the scanning electron micrograph of blend after addition of required quantity of moisture and mixing for 10 min. It can be seen that moisture makes particles to come together and cohesive forces between particles increased. Figure 6 shows the micrograph after 20 min of mixing and this stage is characterized by the disappearance of fine particles. Agglomerates are seen in this micrograph. Figure 7 is the SEM image of blend after mixing for 30 min. A total absence of fine particles is seen in this image and more number of agglomerates was seen. Figure 8 shows the micrograph of blend after addition of moisture absorbents. No major change in the particle size and morphology is seen at this stage. It suggests that added moisture adsorbents adhere onto the existing particles and help in improving flow properties of the granules.[10] Figure 9 shows that granules further gain shape during mixing in the presence of moisture adsorbents and lubricants. Presence of lubricant particles can be seen on the granules. Both of these factors further improve flow properties of granules.

Data for pre- and post-compression parameters for the 50 kg batch is given in Table 7. Both granules and tablets prepared using MADG process showed desirable characteristics thus it implies that MADG process can be successfully scaled up to a batch size of 50 kg. Table 8 gives the comparison of time required for granulation using MADG and wet granulation process. It also gives the comparison in terms of manpower required to execute both the processes. This clearly indicate MADG to be an energy efficient process as less time, energy and manpower is required and is easily scalable too. The present work also establishes Kollidon VA 64 as the binder for MADG process when high drug loading is required.

Table 5: Data of postcompression parameters of formulations prepared by moisture activated dry granulation and wet granulation methods

	F1	F2	F3	F4	F5	FWG
Hardness (kg/cm^2)	3.0	4.0	5.0	5.0	6.0	6.0
Friability (%)	1.0	0.9	0.30	0.28	0.19	0.23
DT (min)	2.0	2.46	7.2	12.5	16.7	4.0
Dissolution (%)	100	98.48	101.8	76.9	35	96.45

Table 6: Effect of the amount of water on precompression parameters of moisture activated dry granulation blends after moisture addition stage

Parameters	F3A	F3B	F3C	F3D
Bulk density (g/ml)	0.44	0.47	0.51	0.56
Tapped density (g/ml)	0.49	0.52	0.57	0.65
Compressibility Index (%)	10.20	9.61	10.52	13.84
LOD (%)	6.13 %	5.07 %	2.03 %	1.63%
Angle of repose	30.00	29.01	31.71	33.33

Table 7: Pre- and post-compression parameters of paracetamol granules and tablets (Batch size 50 kg)

Bulk Density (g/ml)	Tapped Density (g/ml)	Comp. Index (%)	LOD (%)	Angle of Repose	Hardness (Kg/cm^2)	Friability (%)	DT (min)	Dissolution in 30 min (%)
0.58	0.72	19.44	2.96	32.11	3.4	0.3	2.08	89

Table 8: Comparison of moisture activated dry granulation process with conventional granulation process

S no.	Stage	MADG process (min)	Conventional granulation process (min)
1	Material sifting	10	10
2	Dry mixing	5	5
3	Water spraying	10	---
4	Addition of starch (p)	---	10
5	Wet mixing	10	10
6	Semidrying	---	20
7	Milling and sifting	---	20
8	Semidrying	---	30
9	Absorption stage	10	---
10	Final sifting	10	15
11	Lubrication step	10	10
12	Extra time required	20	20
Total time required		80	150
Maximum number of Manpower required for this process		3	6

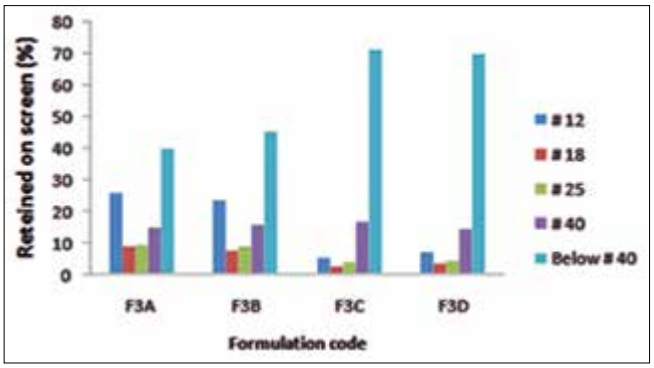

Figure 3: Particle size distribution effect of the amount of water on particle size of paracetamol granules prepared by moisture activated dry granulation process

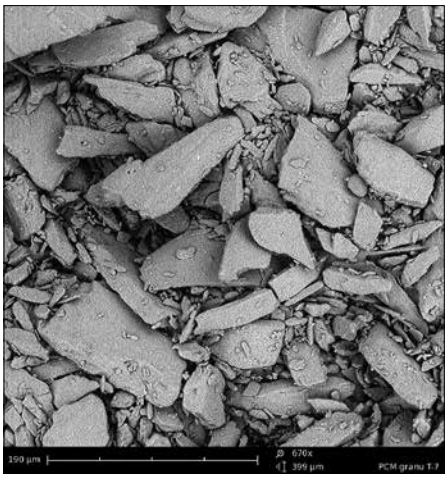

Figure 4: Blend before addition of moisture

Figure 5: Blend after moisture addition stage

Figure 6: After 20 min of mixing

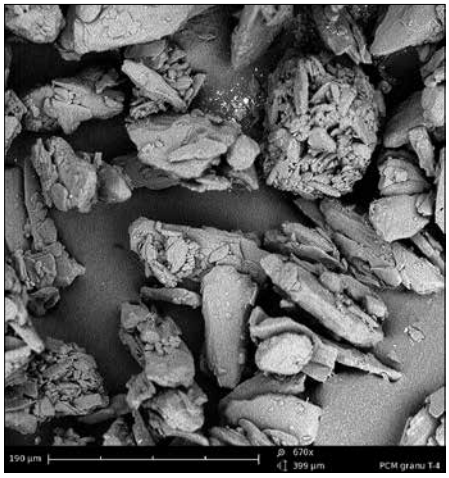

Figure 7: After 30 min of mixing

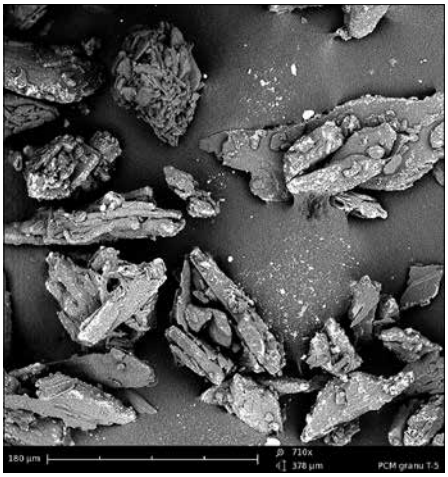

Figure 8: After addition of moisture absorbants

CONCLUSION

The MADG process for preparing PCM tablets was found to be a simple, clean, lean, and robust for particle-size enlargement. The results from the evaluation of the effects of the granulating binder level, binder type suggest that combination of both PVP K-30 and Kollidon VA 64 creates granulation with good physical properties and finished products with desirable quality attributes. The process is applicable for accomplishing most of the granulation need for solid dosage-form development as practiced in the pharmaceutical industry. It is also an economical,

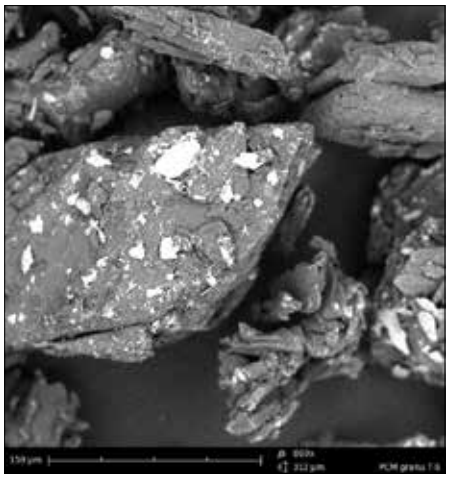

Figure 9: After addition of lubricants

energy-saving, green, and efficient manufacturing process. The PCM tablets prepared by MADG process had advantages such as short manufacturing time and few critical formulation and process variables when compared with conventional wet granulation process.

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