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Effect of Absorbent on Granule and Tablet Properties Prepared by Moisture Activated Dry Granulation Technique

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ABSTRACT

Moisture activated dry granulation (MADG) is a novel process for tablet formulation, known to overcome the difficulties experienced with conventional wet granulation in terms of drying, milling and substance sensitivity towards heat & moisture. In the present study, Metoprolol succinate was used as model drug and the granulation was done by MADG and conventional wet granulation technique. The granules were prepared using SpressB-818 and Prosolv SMCC90 as an absorbent to absorb moisture from the powder blend and redistributing it, thus eliminating one step of drying. In trial batches, the effects of varying concentration of both absorbents were explored. Granules were evaluated for parameters such as amount of fines, drying time, bulk density, compressibility, angle of repose etc. The study indicated that the granules retained their structure in comparison with the conventional process with respect to all the physicochemical parameters and those prepared with Spress-818 were found to superior to Prosolv SMCC90 in terms of some evaluation parameters.

INTRODUCTION

Moisture activated dry granulation (MADG) is a unique method of granulation where, unlike conventional granulation process, granules are formed by moisture and heat is not used for drying of granules. MADG process was introduced in 1987 by Ullah et al. 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. MADG process is considerably less time consuming than a typical wet granulation (Mahida and Gupta, 2013). Thus, MADG technique is most suitable for preparation of solid dosage forms of active substances which are prone to chemical degradation and/or exhibit physical phase transition upon contact with heat and water or aqueous liquids which are used for conventional wet granulation processes (Mitja Stukelj et al., 2011).

The granule formation mechanism in MADG is same as that of in conventional wet granulation. In both cases, it is a process of powder particle size enlargement, often in the presence of water and binders, through wet massing and kneading. The main differences between these two processes are the amount of granulating liquid used and the level of agglomeration achieved. In conventional wet granulation, substantially more water is utilized to create larger and wetter granules followed by heat drying to remove the excess water and milling to reduce the granule size whereas, in case of MADG, only a small amount of water is used to create agglomeration, followed by moisture absorption and distribution. Neither heat drying nor milling is required (Ullah & Wang, 2010). Metoprolol succinate is a drug quite susceptible to degradation by moisture and heat. Therefore in the present study, it was used as a model drug.

The Moisture Activated Dry Granulation involves two major stages

1. Agglomeration

2. Moisture distribution and Absorption Stage. (Gerhardt, 2009; Thejaswini et al., 2013).

A. Agglomeration

In this stage, all or part of the active drug is mixed with filler(s) and an agglomerating binder to obtain a uniform mixture. During mixing, a small amount of water (1–4%) is sprayed onto the powder blend; water droplets hydrate the dry binder and create tacky nuclei or tacky wet mass. The binder works as the drug and excipient move in the circular motion caused by the mixer impellers or blades. Dry powder particles adhere to the wet nuclei or wet tacky mass to create moist agglomerates. The resulting agglomerates are small and spherical because the amount of water used in the MADG process is much lower than that in conventional wet granulation. Thus, agglomerates cannot grow into large and wet lumps. The particle size of the agglomerates generally is in the range of 150–500 µm.

B. Moisture-Distribution and Absorption Stage

In this stage, moisture absorbents are added as mixing continues. When these agents come into contact with the moist agglomerates, they pick up moisture from the agglomerates and redistribute moisture within the mixture. The entire mixture thus becomes relatively dry. This process results in a granulation with uniform particle size distribution (Gerhardt, 2009). In this study, two absorbents namely Spress B818 and Prosolv SMCC 90 were used to determine the more suitable one between these two for Metoprolol succinate tablets.

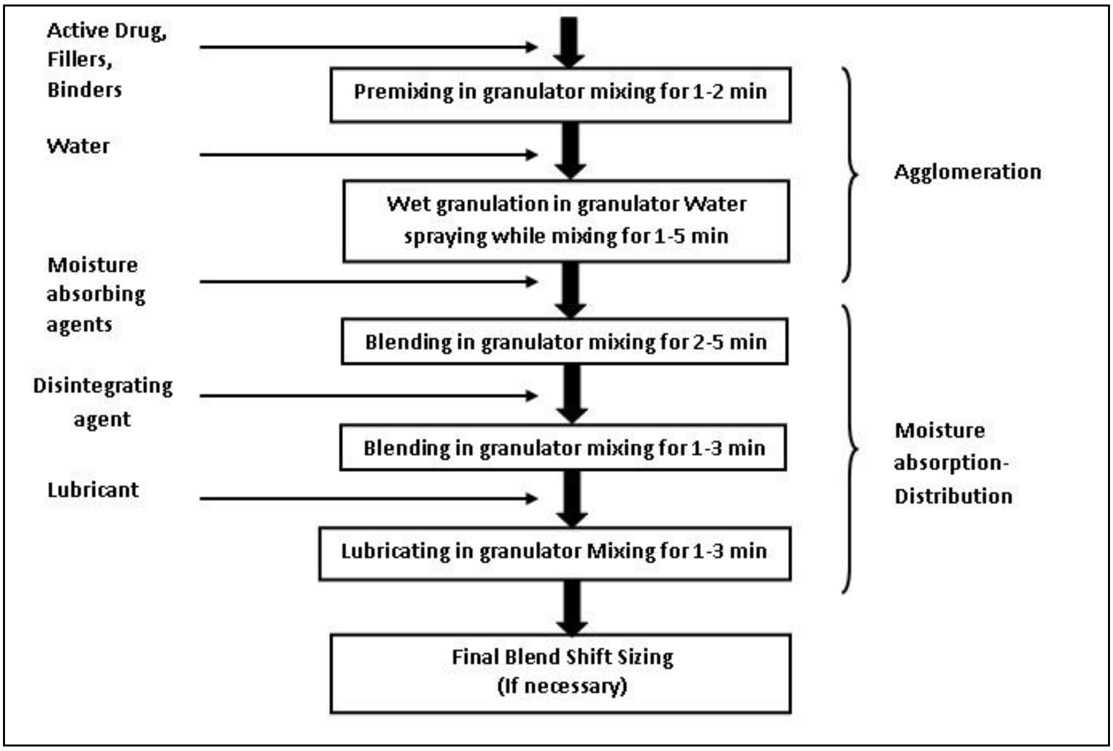

Fig 1: Moisture- Activated Dry Granulation – Formulation Development

MATERIALS AND METHODS

A. MATERIALS:

Metoprolol succinate was obtained as gift sample from Wockhardt Limited, Aurangabad, Maharashtra, India. Lactose monohydrate, Magnesium stearate, Aerosil and PVPK 30 were obtained from Atra Pharmaceuticals, Aurangabad, Maharashtra, India. Maize starch was procured from Qualigens fine chemicals, Mumbai, Maharashtra, India. Prosolv SMCC 90 was obtained as gift sample from Lupin Pharmaceuticals, Aurangabad and Spress B 818 from Grain processing USA.

PREFORMULATION STUDIES

Characterization of Metoprolol succinate, Spress B818 and Prosolv SMCC 90 was done by conventional standard evaluating parameters like color and appearance, melting point, solubility and sophisticated techniques-Fourier Transform Infra red (FTIR), Ultra Violet (UV) spectra and Differential Scanning Colorimetric analysis (DSC) using established procedures.

FORMULATION STUDY

Preliminary trial batches were prepared using Spress B818 and Prosolv SMCC90 for preliminary evaluation (Table 3). The wet granulation batch was also prepared using above formula to compare with MADG batch.

Table 1: Preliminary trial batches:

Ingredients for tablet	Quantity in each Formulation (mg/tab)						
	A	**B**	**C**	**D**	**E**	**F**	**WG**
Metoprolol Succinate	50	50	50	50	50	50	50
Lactose monohydrate	169.38	166.38	164.38	169.38	166.38	164.38	169.38
Maize starch	12.5	12.5	12.5	12.5	12.5	12.5	12.5
PVP K-12	5	5	5	5	5	5	5
Water	0.2	0.25	0.5	0.2	0.25	0.5	-
Sprees® B 818	5	8	10	-	-	-	-
Prosolv® SMCC 90	-	-	-	5	8	10	-
2% starch paste	-	-	-	-	-	-	q. s.
Aerosil	3.12	3.12	3.12	3.12	3.12	3.12	3.12
Magnesium stearate	5	5	5	5	5	5	5
TOTAL	250	250	250	250	250	250	250

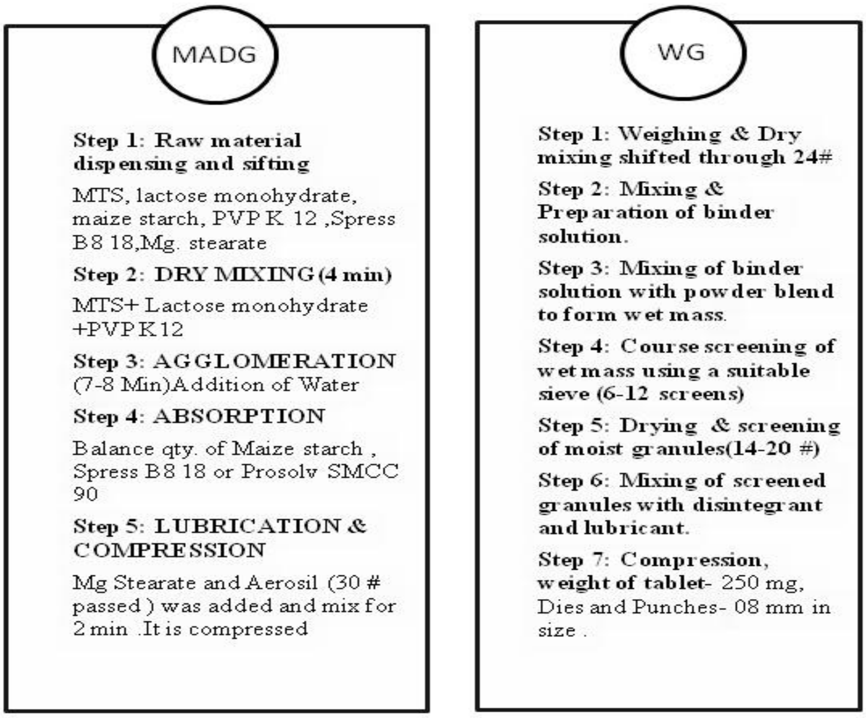

Fig. 2: Overview of MADG versus WG

RESULTS AND DISCUSSION

FORMULATION STUDIES

Pre-compression Characteristics of Powder Blend

From the powder characteristics i.e. angle of repose, compressibility index and Hausner's ratio etc., it was concluded that the powder possesses excellent free flowing characteristics.

Table 3: Flow properties of preliminary trial batches powder:

Parameters	F1	F2	F3	F4	F5	F6
Bulk Density	0.282 ± 1.04	0.289 ± 1.02	0.296 ± 1.14	0.287 ± 1.52	0.313 ± 1.88	0.307 ± 1.93
Tapped Density	0.342 ± 1.07	0.358 ± 1.17	0.365 ± 1.47	0.345 ± 1.97	0.342 ± 1.67	0.345 ± 1.57
Carr's Index (%)± SD	18.01 ± 1.83	19.14 ± 2.83	19.09 ± 4.13	16.85 ± 5.35	20.94 ± 4.81	17.83 ± 2.73
Hausner Ratio (%)	1.245 ± 1.02	1.231 ± 1.04	1.235 ± 1.08	1.206 ± 1.048	1.267 ± 2.02	1.225 ± 2.01
Angle of Repose(^{0})	19.17 ± 1.12	18.17 ± 1.62	16.58 ± 1.92	24.59 ± 1.12	23.27 ± 1.99	26.17 ± 2.12
Loss on drying (%)	2.160	3.482	2.34	3.08	4.56	4.95
Amount of Fines (%)	10.24	12.32	12.99	14.24	15.07	14.97
Drying Time (Minutes)	2.0	2.5	2.8	3.1	3.8	4.2

(All the values are represented as mean ± s.d; n=3)

The above data shown amount of fines of spress B818 was within 10 to 12% while prosolv shows 14 to 15%. The drying time for Spress batch was found less than that of Prosolv batch. The parameters like loss on drying and angle of repose also proven the superiority of Spress batches over Prosolv formulation batches.

Evaluation of Tablet Characteristics for Preliminary batches:

- **Physical Appearance:**

The tablets were observed visually for their physical appearances: such as colour, texture and found that all the formulations were of good appearance having white to yellowish white colour and smooth surface texture.

- **Parameters for Tablet Evaluation:**

Formulated batches of tablet were evaluated for hardness, weight variation, thickness and diameter, percent friability, content uniformity, The results of all these were in compliance with specification of I.P. are indicated in Table 4.

- **Hardness and Friability:**

The formulation showed hardness value in the range of to 4.16 to 5.08 Kg/cm^2. Another measure of tablets strength is friability. In present study, the friability value for all tablet formulation was found to be less than 1% indicate that the friability within the prescribed limit.

- **Thickness and Diameter:**

Thickness of all tablet formulations was found to be 2.33mm and diameter of the tablets were found to be in the range of 8.01 to 8.03 mm.

- **Drug Content Uniformity:**

The drug content of all formulations was found to be in the range of 98.5 and 102.62 %, which was found satisfactorily within I.P., limits (not less than 90% and not more than 110%).

Table 4: Evaluation of Tablet Characteristics for Preliminary batches

Parameters	F1	F2	F3	F4	F5	F6
Hardness(Kg/cm^2)±SD	3.92±	4.08 ±	4.65 ±	4.20 ±	5.16 ±	4.72 ±
Diameter (mm) ± SD	8.01 ±	8.02 ±	8.01 ±	8.03 ±	8.02 ±	8.01 ±
Thickness (mm)± SD	2.32 ±	2.30 ±	2.34 ±	2.31 ±	2.30 ±	2.33 ±
Friability (%)± SD	0.57 ±	0.51 ±	0.68 ±	0.72 ±	0.79 ±	0.53 ±
Disintegration time (Min)	8.1	8.3	8.6	12.3	12.9	13.1

- **Weight Uniformity:**

The Pharmacopoeial limits of deviation for tablets of more than130mg and less than 324mg are ± 7.5 %. The average percentage deviation for all tablet formulations was found to be within the specified limits and hence all formulation complied with the test for uniformity of weight.

- **Evaluation of % cumulative drug release.**

Drug release that is cumulative percentage of drug dissolved in phosphate buffer pH 6.8 for the period of 60 minutes at temperature 37°C was studied. Volume of dissolution media was 900 ml. Samples 10 ml each were withdrawn after every 5 minutes up to 60 minutes. To maintain the volume in dissolution vessel, 10 ml of fresh solution was replaced in each case after withdrawal of the sample and analyzed by using U.V. Spectrophotometer at 222nm wavelength and values were reported in Table 5.

- **Dissolution medium:** pH 6.8
- **Apparatus:** USP type II paddle
- **Speed:** 50 rpm
- **Volume of dissolution medium:** 900 ml

Table 5: Cumulative % drug release for preliminary trial batches of tablet formulation.

Sr. No.	Time in Minutes	Cumulative % drug release					
		A	B	C	D	E	F
1	5	8.102 ± 1.25	20.854 ± 0.53	22.501 ± 0.89	21.24 ± 0.40	19.82 ± 0.96	8.77 ± 0.68
2	10	12.604 ± 1.35	29.364 ± 0.98	33.021 ± 0.57	32.44 ± 1.23	28.86 ± 1.35	14.76 ± 1.25
3	15	17.847 ± 1.53	30.801 ± 1.23	42.904 ± 1.20	42.32 ± 0.58	30.66 ± 1.68	17.12 ± 1.48
4	20	31.971 ± 2.25	36.683 ± 2.25	51.704 ± 1.48	51.94 ± 2.50	40.62 ± 0.24	20.74 ± 2.04
5	25	34.121 ± 1.40	41.712 ± 1.27	59.262 ± 0.69	59.42 ± 1.87	43.25 ± 2.68	32.04 ± 2.15
6	30	35.384 ± 1.25	42.774 ± 0.78	66.384 ± 2.05	66.51 ± 1.33	45.34 ± 0.87	34.74 ± 1.78
7	35	37.372 ± 3.42	44.174 ± 1.44	75.603 ± 3.80	73.05 ± 2.87	46.82 ± 0.98	36.22 ± 0.98
8	40	38.731 ± 1.02	46.474 ± 2.39	78.382 ± 1.44	77.42 ± 3.01	52.24 ± 1.75	37.85 ± 0.65
9	45	45.862 ± 0.86	52.825 ± 2.98	85.250 ± 1.87	85.26 ± 1.67	63.22 ± 1.36	46.82 ± 1.48
10	50	45.866 ± 2.24	61.043 ± 2.12	91.160 ± 0.98	90.42 ± 0.58	66.61 ± 1.25	48.86 ± 0.94
11	55	49.662 ± 1.22	67.443 ± 1.43	97.953 ± 0.76	96.36 ± 1.23	68.42 ± 0.49	48.88 ± 1.36
12	60	51.662 ± 1.07	69.664 ± 1.56	99.056 ± 1.77	99.01 ± 1.85	72.46 ± 1.47	50.46 ± 1.11

(All the values are represented as mean ± s.d; n=3)

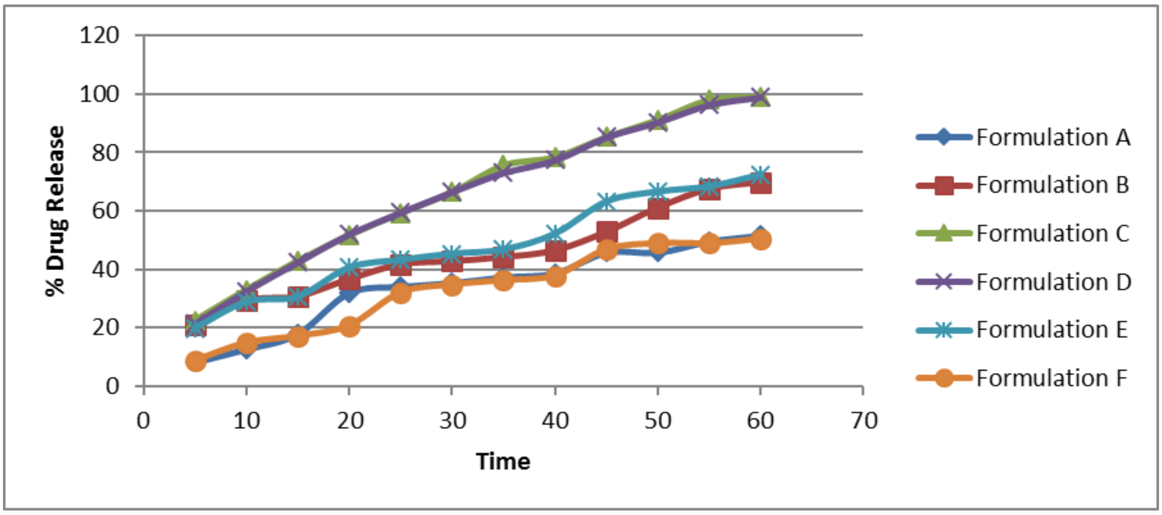

Fig. 3: Dissolution of Trial Batches

It was found that maximum drug release was exhibited by formulation C and D, which was prepared by using Spress B818 and Prosolv SMCC 90 respectively. This was followed by formulations E, B, F and A respectively. This shows that tablets prepared using higher concentration of Spress B818 and lower concentration of Prosolv SMCC 90 exhibited similar dissolution properties. However, increasing the concentration of Prosolv SMCC 90 did not improved dissolution.

CONCLUSION

Numerous active substances are sensitive to the heat and presence of relatively high amount of moisture. Moisture may stem from the excipient used in the formulation or from the manufacturing process, e.g. aqueous granulation, this can pose significant problems in the manufacturing of pharmaceutical formulations and dosage forms containing such active substances. So the presence of moisture or requirement of heat as processing parameter is particularly undesirable if the active substance is prone to chemical degradation and/or physical phase transitions into an undesired crystalline and/or amorphous form (polymorphism) when being in contact with water or water- containing solutions. So MADG is developed to overcome these problems by eliminating one step of drying.

The time taken to prepare tablets was considerably less with MADG as compared to conventional wet granulation technique. It was found that batches prepared using both absorbents Prosolv SMCC 90 and Spress B818 were in compliance with pharmacopoeial limits. However, there were certain differences which proved superiority of Spress B818 over

Prosolv SMCC 90 like amount of fines in granules, drying time, loss on drying and angle of repose. Thus, Spress B818 can be used for optimization of the formulation instead of Prosolv SMCC 90.

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