J-STAR RESEARCH, Inc

Process Simplification Series No. 1

Moisture-Activated Dry Granulation (MADG) – An Economical Alternative for Wet- and Dry-Granulation

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Abstract

Wet granulation, dry granulation and direct blending are the three most common granulation processes for solid dosage form production in the pharmaceutical industry for decades. However, each of the three mentioned process has its drawbacks, among which, the requirement of post-granulation operations is one of the major weakness. Drying for wet granulation and milling for dry granulation both add complexity to the granulation processes which require more equipment and human efforts. The potential segregation for direct blending also adds more risks to the material handling and final content uniformity. Moisture-activated dry granulation (MADG) is an economical and novel granulation process which only requires minor amount of liquid (1-5%) to trigger the agglomeration of particles, uses the high shear granulator to spread out the moisture and then form uniform granules without subsequent drying or milling process, which can save the cycle time tremendously. In addition, due to the limit amount of liquid required during the MADG process and the absence of drying and milling, this process minimize the risk of making different forms of API and amorphous content, which is an advantageous granulation method for heat-sensitive and water-sensitive Active Pharmaceutical Ingredients (APIs) and formulations.

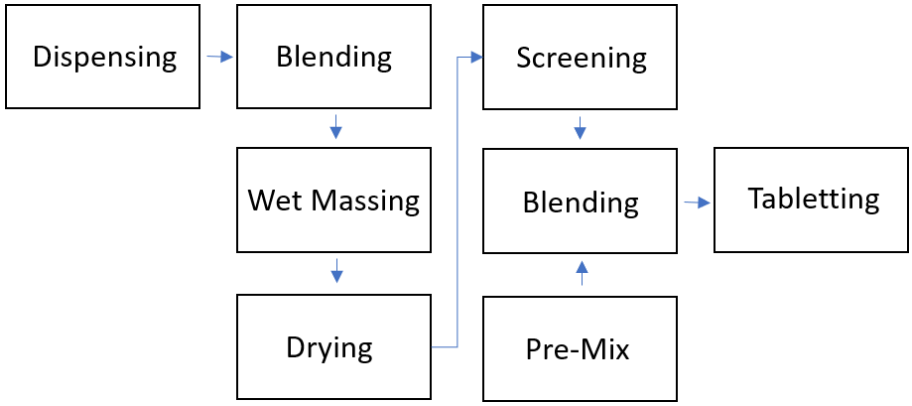
Introduction

Granulation is one of the most critical unit operations in the production of pharmaceutical oral dosage forms. Wet granulation, dry granulation and direct blending are the most common granulation processes in pharmaceutical industry. However, as being widely practiced, concerns and drawbacks for each process have also been developed.

One of the major drawbacks for wet granulation and dry granulation processes is the requirement of extra steps to be applied after each granulation process, such as drying for wet granulation and milling for dry granulation. In addition to adding complexity and cost to the production line, these extra steps also set limitations to the APIs and excipients to be granulated since wet granulation would require a decent amount of liquid addition, drying and milling would generate massive heat to the granules, which are not friendly to heat- and water-sensitive APIs.

Moisture-activated dry granulation (MADG) is a novel and economical granulation process, which was first brought up more than 30 years ago[1], but it has not raised wide attention. It utilizes a similar setup to a high shear granulator but only requires small amount of water (1 – 5%) to activate the agglomeration formation, after which, the process uses stepwise addition and blending of the pharmaceutical ingredients that absorb and distribute the moisture, thus creating a uniform, free-flowing and compatible granules[2]. Figure 1 compares detailed steps between a traditional high shear wet granulation (a) and MADG (b)[3].

(a)



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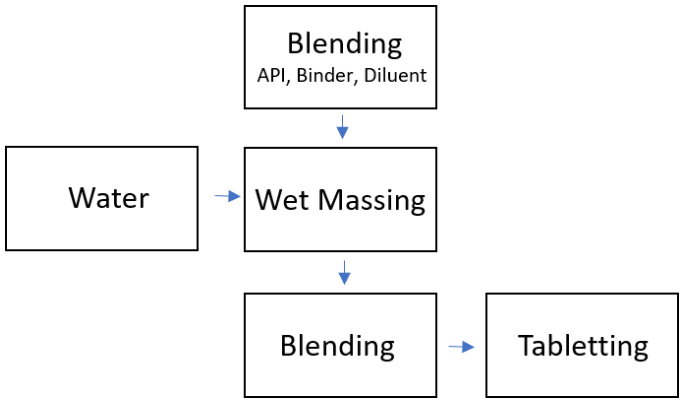


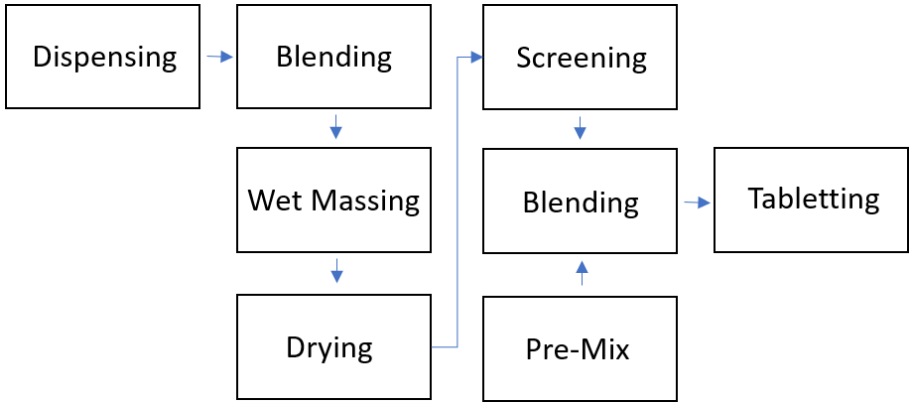
Fig. 1. Process steps involved in (a) traditional wet granulation, (b) the MADG[3].

Given the simplicity, and cost-saving potential of MADG process, it can be a good alternative for wet and dry granulation in pharmaceutical industry. Chen et al. published a study comparing the MADG process with the conventional granulation processes for sematilide hydrochloride tablets4. The authors found that not only the MADG was able to make comparable granules but also showed better flowability and tablet-content uniformity. Ullah et al. has further demonstrated and developed the MADG process by providing a step by step-by-step procedure for the MADG-based formulation development and evaluated the effects of the formulation and process variables on the MADG process[5]. Takasaki et al. has studied the water activity on granule characteristics and tablet properties produced by MADG[6]. This article gives a brief demonstration of the MADG process along with a review of the recent development of this technology.

The MADG Process

The MADG process can be conducted using a regular high-shear granulator, where some optimization needs to be done on the spraying nozzle (droplet) to achieve uniform granules. The objective of this process is not to make large particles but rather to agglomerate the fines and bind the drug with excipients to make good-flowing, compactible granules. The key for this technique

(a)



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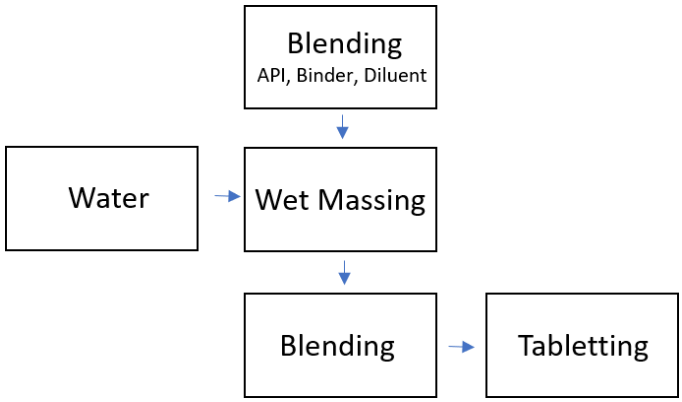

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is to add just enough of water to achieve particle's agglomeration rather than adding excess water that would require further drying.

The MADG process includes two major stages, the agglomeration stage and the moisture distribution and absorption stage. During the agglomeration stage, the API is first blended with filler and binder to obtain a uniform mixture as dry blends. A small amount of water (1-5%) is then sprayed in the form of small droplets onto the dry blends while blending, which moistens the blend and activates the binder to form agglomeration between particles. The major advantage of this MADG process is that only a small amount of water is required, so it does not required milling and drying afterwards, which other granulation processes normally do. In addition, the resulting agglomeration during this stage are small and aspherical because the amount of water used is much lower than conventional wet granulation therefore the agglomerates cannot grow into large, wet lumps. The second stage is the distribution and absorption stage when the water insoluble filler component such as microcrystalline cellulose (MCC) or silicon dioxide are added while blending to absorb and distribute the moisture to form relatively uniform and dry granules. At the end, disintegrant and lubricant can be added during blending as needed[7,8]. A detailed step-wised operations are described in Figure 2. The MADG process only take 10-20 minutes excluding material loading, even for a commercial-scale batch.

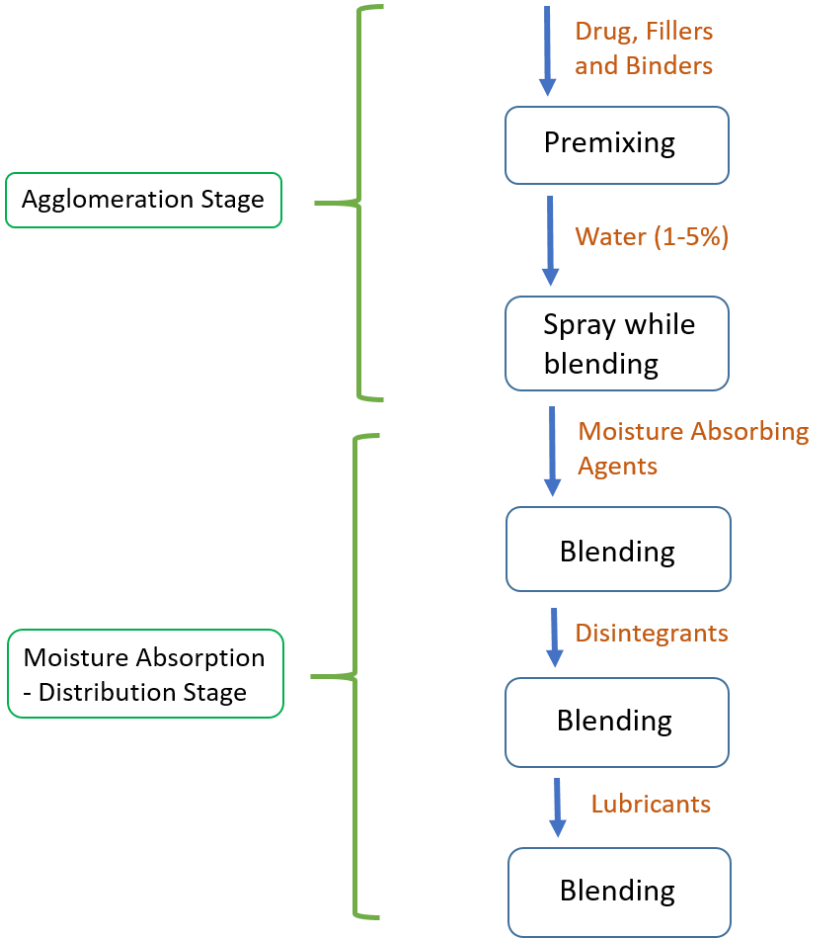

Fig. 2. Step-wised flow diagram of the MADG process.

Excipients Selection

MADG has been proved to work for a wide range of APIs with varying properties and attributes for different drug loads, even it is higher than 80%. Also, researchers across the world has found that MADG based formulation shows a comparable dissolution performance to commercial formulations[8]. However, good selections of excipients in the formulation are essential to achieve success.

Fillers and Binders

Unlike the conventional wet granulation, MADG process employs nonabsorbent and easy-to-wet fillers such as lactose monohydrate and mannitol instead of microcrystalline cellulose or starch. The reason for this is that MCC and starch-based excipients absorb and retain a considerable amount of moisture thus increase the total amount of water required for the MADG process. However, if a high drug-load is designed then MCC and starch can help avoid over-wetting and over-granulation. In addition, the selected fillers are better not be too coarse or too fine since coarse particles are not easy to agglomerate and fine particles requires more moisture.

The binder used in the MADG process should be wet easily with a small amount of water. Work from researchers has indicated that a low-viscosity polyvinylpyrrolidones (PVP) such as PVP K-12 is ideal for this role. Other suitable binders include hydroxypropyl cellulose (HPC), copovidon, maltodextrins, sodium carboxymethylcellulose (Na CMC) and hydroxypropyl methylcellulose (PHMC). The binders can be used singly or in combinations to achieve desired granules or avoid specific concerns.

Moisture absorbents

The moisture absorbents also play critical roles in the MADG process to absorb the remaining moisture and also maintain the entire batch (agglomerates and nonagglomerated excipients) within a good particle size distribution. So the moisture absorbents are desired to be selected at a closer particle size to the agglomerates from the earlier stage. MCC Avicel PH 200 (FMC, Philadephia), low moisture excipient with a particle size around 200 μm, which is a good fit as both filler and moisture absorbent. Aeroperl 300 from Evonik (Essen, Germany), a commonly used free-flowing silica is also a good option for moisture absorbents. Only a small amount of Aeroperl 300 is needed in MADG process which is advantageous from preventing tablet-ejection problems. If these two are not available, researcher has also recommended regular microcrystalline cellulose (e.g. Avicel PH101, PH102) and regular silicone dioxides as substitutes.

In some of the cases when the drug itself are soluble and becoming tacky during moistening, the moisture absorbents can be added in the agglomeration stage to spread the moisture.

Disintegrants and Lubricants

A coarse size of Crospovidone has been recommended as the disintegrant in MADG process. One of the commonly used lubricants, magnesium stearate, also works for MADG.

Optimization of MADG Process

The quality of the final MADG products can be impacted by formulation, droplet size and the scale of process. Therefore, the proper MADG process needs to be developed based on different cases.

Binder selection and binder level play a critical role in the agglomeration stage during the MADG process. PVP K-12, HPC EXF, Copovidone are some of the commonly used binders which have been proved to be successful for MADG process, however, different binders have been found various results in terms of the final particle size distribution for different formulations. In addition, larger amounts of binder require more water to hydrate thus would increase the water addition amounts to form good agglomerations.

Droplet size is another significant factor for MADG. Large and ununiformed particle size of droplet may result in ununiformed granule sizes. When the droplet size is small enough (lower than 110 μm), study has shown that it would reduce the impact of spraying, which indicates that the high shear blending can nicely spread the water if the droplet is relatively small.

The MADG process has been successfully scaled up to 30 kg batch to obtain final blends with similar quality attributes[5].

Conclusion

The MADG has been proved to be a simple, robust and economical process. Short cycle time, few critical process variables, suitable for water- and heat-sensitive drug substances make it a good alternative to wet granulation and dry granulation processes.

References

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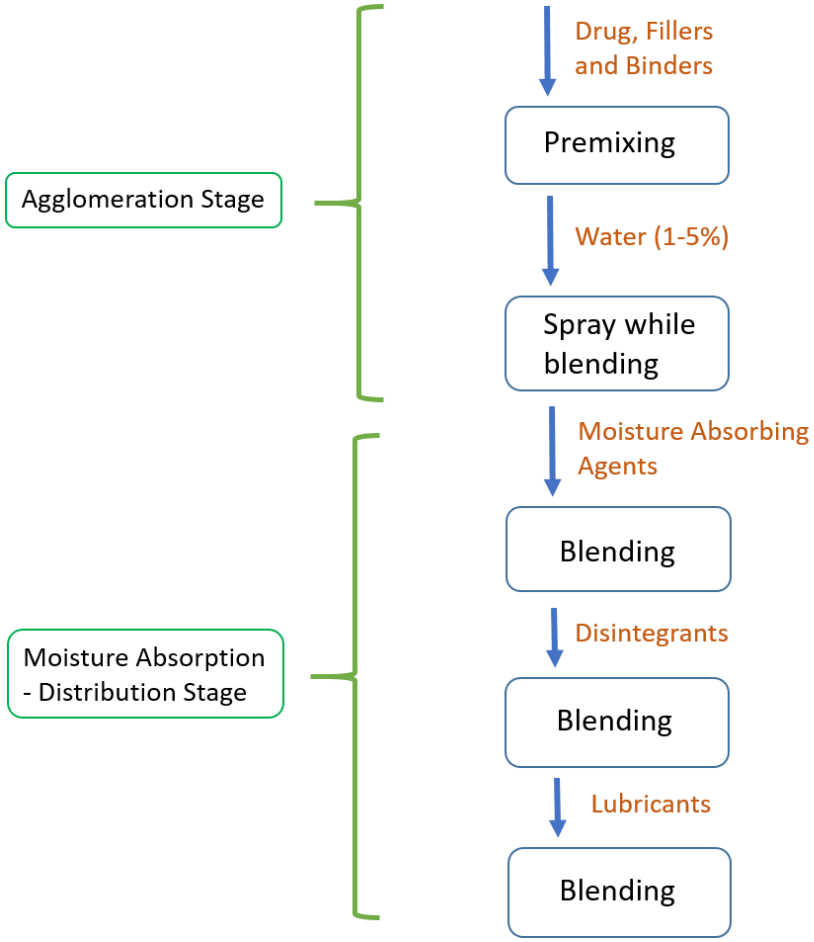

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