Process Simplification Series No. 1

Moisture-Activated Dry Granulation (MADG) – A Simplified Process to Replace Wet- and Dry-Granulation

Drug Product Development, February 2021

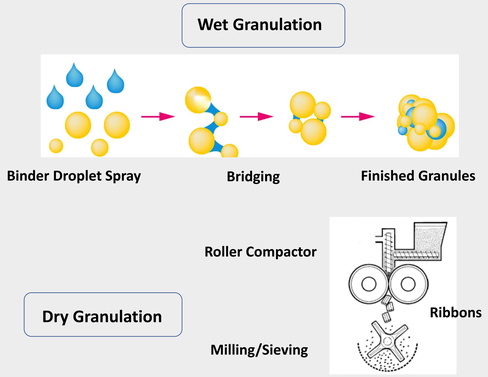
OUTLINE

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.

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.

BACKGROUND

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. Figure below demonstrate the granulation method of wet and dry granulation



Disadvantages of Wet and Dry :

Wet Granulation	Dry Granulation
Requires extra steps of drying and milling	Heavy duty equipment (roller compactor)
High cost (cycle time, labor and energy)	Generation of dust causing contamination
Not suitable for thermolabile materials	Extra step of milling
Not suitable for moisture-sensitive materials	Segregation of Components
Oversized Granules	Powder flow issues
	Soft tablets (difficult for film coating)

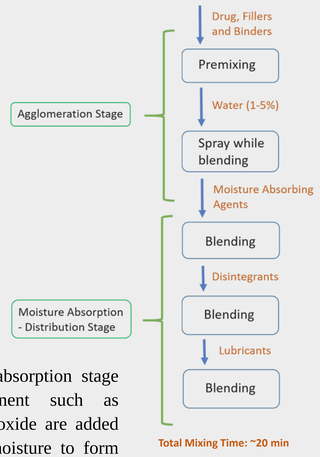
THE MADG PROCESS

Moisture-activated dry granulation (MADG) is a novel and economical granulation process, which was first brought up more than 30 years ago1, 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.

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 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.



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.

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 have 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 require 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. Therefore, 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, Philadelphia), 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.

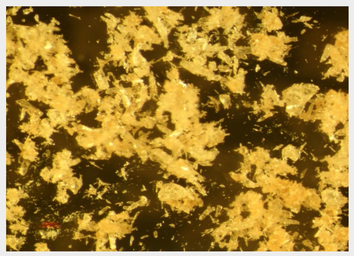
In some of the cases when the drug itself are soluble and becoming tacky during moistening, the moisture absorbents can be added in the agglomeration stage to spread the moisture.

Disintegrants and Lubricants

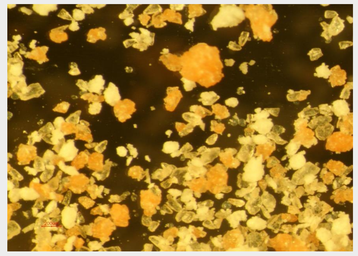
A coarse size of Crospovidone has been recommended as the disintegrant in MADG process. One of the commonly used lubricants, magnesium stearate, also works for MADG.

RESULTS FROM LITERATURE

Characterization of MADG Product
- High Dose Formulation (65% of API)



Starting Blends



MADG Prodcuts

	Moisture Content (%)	Flowability (ml/s)	Pellet hardness (scu)
Starting Blends	1.0	1.9	21.8
MADG Products	1.9	8.3	20.6

- Researchers were able to achieve uniform MADG granules with significant improvement in flow properties and minor moisture content and tabletability changes

Image Source: Ullah, Ismat, Jennifer Wang, Shih-Ying Chang, Hang Guo, San Kiang, and Nemichand B. Jain. "Moisture-activated dry granulation part II: the effects of formulation ingredients and manufacturing-process variables on granulation quality attributes." *Pharmaceutical technology* 33, no. 12 (2009): 42-51

SUMMARY

- MADG is an economical and novel granulation process, which can be achieved by a general high shear granulator/blender. It is a simple, clean and lean process.
- MADG only requires minor amount of liquid (1-5%) to trigger the agglomeration of particles.
- It is a robust one-step process, which does not require drying or milling afterwards, which makes it economical, energy saving and environmentally friendly process.
- It is applicable to most of the granulation needs of pharmaceutical industry.
- There is no heat and large quantity of liquid applied to it, which makes it applicable for heat and moisture sensitive APIs.
- MADG is easy to be scaled up and transferred to continuous process.

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