In the pharmaceutical industry, the three most common production processes for solid dosage form production are wet granulation, dry granulation (roller compaction) and direct blending. Yet, despite being well-established techniques, each has its drawbacks. Moisture-activated dry granulation (MADG) was developed in response to the difficulties experienced with wet granulation, in terms of endpoint, drying and milling, and offers an efficient, cost-effective granulating process that does not require a drying step.

The old adage that “time is money” has never rung truer. Manufacturers are increasingly aware of processing steps, production costs, safety issues and time-to-market, not withstanding the absolute requirement for quality and reliability. In tablet manufacture, direct compression has always been the traditional first choice, followed by granulation, which adds time and cost to the process (and formula).

A growing, but not as yet widely adopted process, is moisture-activated dry granulation (MADG): as minimal moisture is needed in this specialty granulation process, no drying time is required, significantly shortening the processing time. It’s a simple and innovative process in which granules are created with water and a granulating binder, as in wet granulation, but are not heat dried or milled, which also helps to minimise endpoint sensitivity. Plus, it works in situations when wet granulation or dry compression won’t (such as water- or heat-sensitive products). And, along with reduced steps, the equipment required is the same as that used in traditional wet granulation – which is what most manufacturing sites are equipped with – so mass implementation would be relatively easy to achieve.

The benefits of wet granulation are well known, and include good particle size distribution and good flow. It’s a flexible technique that offers good uniformity and a wide range of applications. Yet, it lacks robustness, requires multiple steps, milling, an expensive drying step and there is a risk of over-granulation. Where MADG comes to the fore is that it is an efficient, cost-effective granulating process that does not require a drying step; that is, moisture is used to activate granulation, but the granules are not heat dried. Essentially, the process comprises two major steps: agglomeration and moisture distribution. During agglomeration, the active pharmaceutical ingredient (API) is dry blended with a binder or combination of binders in a typical high shear granulator. A limited amount of moisture (8%) is then added to granulate the powder mixture, but not enough to over-wet it. The water droplets hydrate the dry binder(s) and create tacky nuclei or a tacky wet mass, and the dry powder particle adhere to the tacky nuclei/ mass to create moist agglomerates. During the moisture distribution stage, an absorbent excipient is added to evenly distribute the moisture and ‘dry’ the granulation. At this stage, it is still possible to add in any remaining drug or, if the formulation requires it, a lubricant or disintegrant. Finally, the contents can be lubricated, sieved/ sized and blended, although, in reality, limited or no sizing is required in this process because the particles are small and uniform (Figure 1).

The process only takes about 10–15 minutes and the final granulation looks like a direct blend formulation with fine particle size distribution. In this process, the drug is bound with the ingredients, as in wet granulation, which minimises the potential for segregation. In short, MADG has the best attributes of dry blending and wet granulation, with the caveat that it is just a simpler process to create granules without heat drying and milling. As with any solid dosage form, granulation and any resulting tablet and capsule characteristics will depend on the formula composition.
In terms of equipment, a high shear granulator is more suitable for MADG, and an ideal machine should have efficient impellers/blades and choppers to allow good mass movement and proper mixing. It should also allow water to be sprayed only on the powder bed and not on the blades, choppers or granulator wall. Also, the blades and bowl configuration should be such that it does not allow ‘wet pockets’ or ‘dead spots’ to remain after the moisture distribution or absorption stage, which would then necessitate additional sizing and shifting of the granulation.

**Advantages and Benefits**

Dr Gerard Thone, North/Latin America Technical Services Manager, FMC Biopolymer, in his presentation, ‘MADG: A Low Cost/High Efficiency Approach to Wet Granulation’, observed that MADG produces granules that are very homogenous and free flowing, the amount of remaining water was comparable with a direct compression granulation and the amount of time saved (compared with a typical wet granulation process) was in the order of hours not minutes. Other notable advantages include its suitability for continuous processing, the very few variables involved – resulting in less need for expensive process analytical technology (PAT) – and its applicability to a number of formulations, including high/low drug load formulations, polymer matrix-type controlled release formulations and both soluble and insoluble drug formulations (notwithstanding opportunities in the food and nutraceutical sectors). Using very little energy, it’s a ‘green’ technology with extremely wide scope in the life science manufacturing industries. It is reproducible and scalable, lean and, providing good content uniformity, it’s a better option than conventional wet or dry granulation processes with which to implement the US Food and Drug Administration’s Quality by Design concepts (Table I).

**Discussion**

Although many MADG proponents see no downside to the process and believe it to be a superior alternative to traditional granulation techniques, it is not without its drawbacks. There is still some discussion concerning its use for moisture-sensitive drugs or high drug load moisture-absorbing APIs and there could be other issues with the API, with high drug load formulations being particularly difficult to develop. However, at a less tangible level, there is still some industry resistance to change; being less familiar with the process, there is some apprehension towards adoption. Big Pharma is traditionally risk averse and MADG goes against perceived knowledge and wisdom. But, conversely, there are major benefits for companies looking to scale up; there is a much lower chance of failure compared with wet granulation, which users and customers will find very attractive. It also gives you greater control over the formulation and solves a number of dissolution problems because of the amount of water involved.

Robert Armstrong, a Formulation Development Scientist at Aesica, explained: “A client tried to produce some really small tablets using pneumatic dry granulation and failed. We used MADG and succeeded. And, to cite a specific example, MADG also made it possible to produce Metformin when other techniques failed.” Metformin hydrochloride is an API that not only exhibits batch-to-batch variability but also demonstrates different physical characteristics between suppliers. The challenge was to produce a sustained release tablet that was smaller or, at best, no bigger than what was currently available on the market. Cost was the second factor; therefore, process time and processing technology would also have an impact on how successful the end result would be. The variable nature of the API ruled out a simple blend and direct compression process. Although this is by far the cheapest process, the tablet size would have been too large to accommodate the amount of excipients required to dilute out any API effects. Wet granulation was an option, but processing time and cost of processing was an issue. Metformin hydrochloride is widely available as a generic tablet and is therefore in a competitive marketplace. Newer dry granulation technologies did prove to be partially successful; however, the tablet size was slightly larger than target and the yields were quite low, pushing up the processing time and cost of processing. In addition, the granule characteristics were suboptimal as flowability was not as desired. Using the MADG process, we were able to successfully produce tablets from two different sources of API. The tablets produced weighed 1190 mg in total – containing 750 mg of active – and measured 17 x 9 mm. Currently available 750 mg extended release formulations are 19.0–21.0 mm diameter round tablets, which are physically much larger and very difficult to swallow.
Commercially, as well, MADG offers quantifiable benefits regarding waste reduction, energy use and overall efficiency. In clinical trials or bulk manufacturing, MADG can halve the production time to manufacture compressible granules. The requirement for fluid bed drying is completely removed. Benefits include significantly reduced processing times compared with traditional wet granulation, improved yields with no losses in transfer or fluid bed drying and reduced costs in terms of both energy and work hours. Offering a simple, ‘one pot’ processing approach, less equipment is needed and, therefore, set up is both simpler and more cost-effective. Robert Armstrong commented: “A small-scale development batch was manufactured for a particular product; traditional wet granulation took the best part of a day to manufacture the granule and finish processing it to a point whereby it could be compressed the following day. The MADG process for this product enabled us to manufacture the granule and compress it during the same morning.”

**Conclusion**

MADG is a simple, economical, clean, lean and robust process that creates granulation with very good physical properties and finished products with satisfactory quality attributes. It is applicable to many of the pharmaceutical industry’s granulation needs for solid dosage form development and can be described as a ‘one pot’ granulation process. MADG also offers energy savings, a short manufacturing time and fewer critical formulation and process variables. Of course, with any ‘new’ technology, there is still room for improvement. This could be in the form of multifunctional excipients, which would simplify the process and make it even more economical; for instance, an excipient could be developed that is both a moisture absorbent and a disintegrant, or a moisture absorbent, a disintegrant and a dry binder. And, the development of specialised granulators for MADG, as well as continuous processors and feeders, will also be beneficial. In short, though, MADG increases manufacturing efficiencies, achieves higher asset utilisation, decreases costs and achieves higher yields with fewer fines. Surely, based on these criteria, traditional granulation techniques have a serious alternative.

**Bibliography**

Table I: Summary of MADG benefits.

<table>
<thead>
<tr>
<th>MADG Vs WG</th>
<th>Primary Benefit</th>
<th>Secondary Benefit</th>
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<tbody>
<tr>
<td>Lower amount of added moisture (4% to 8% total)</td>
<td>No drying</td>
<td>Faster process, increased efficiencies, lower production costs</td>
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<tr>
<td>Single production equipment (high shear granulator)</td>
<td>Lower investments and maintenance</td>
<td>Increased efficiencies, lower production costs</td>
</tr>
<tr>
<td>No equipment change</td>
<td>Reduces process time</td>
<td>Lower production costs, faster product development, faster to market</td>
</tr>
<tr>
<td>No milling required</td>
<td>No fines</td>
<td>Higher yields, lower costs</td>
</tr>
<tr>
<td>Lower tablet capping (common w/low moist)</td>
<td>Lower tablet rejection rate</td>
<td>Higher yields, lower costs</td>
</tr>
<tr>
<td>No over or under granulation</td>
<td>Fewer scrapped batches</td>
<td>Higher asset utilisation, lower costs</td>
</tr>
</tbody>
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Figure I: The moisture-activated dry granulation process.