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White Paper

Conical Milling: How to effectively scale-up from lab to pilot to production

Scale-up milling is an important consideration when looking to introduce a new pharmaceutical product, or make changes to an existing formula.

The testing should aim for a particular particle size distribution by identifying the correct tooling setup, as well as flagging potential issues that occur when milled under certain conditions.

Starting with a small scale machine enables the laboratory testing of these variables, without sacrificing large amounts of expensive material during the trial-and-error process.

Once a suitable setup has been selected, this can be tested on a slightly larger machine under pilot plant conditions; this helps to identify potential scale-up deviations. The aim is to finalise screen / impeller combination, machine speed and even room conditions, before committing to production.

Finally, the product can move to production. The previous trials will help expedite the validation process, minimising downtime before production can begin.

This white paper will help provide structure and guidance. A well designed scale-up will save time and money, while improving the overall chance of eventual production success.

Introduction

In many pharmaceutical processes, what works in the lab doesn't always scale-up seamlessly into production; this is true in conical milling. Larger batches, different process conditions, and varying material characteristics can all create unforeseen problems that ultimately impact performance. Despite this, lab and pilot milling can still be a great indicator of scale-up output, and certain steps can be taken to maximize the likelihood of successful production. Certainly, when undertaken correctly, small-scale milling can give an extremely accurate forecast of eventual particle size, shape and machine capacity.

This white paper will aim to help you scale-up with minimum disruption or deviation. While there is no silver bullet, identifying potential pitfalls while understanding best practice can at least provide a logical road map for achieving milling success.

Objective of Scale-Up Milling

The particle size and shape of material is vital to the production of pharmaceutical products. These variables are affected by the original ingredients, their physical and molecular interactions, and the processes they encounter. Milling is the primary procedure used for size reduction of particles prior to tablet and capsule formation. Material is broken down into smaller, more consistent particles, which will be later blended, compressed and coated into the final dosage unit.

The aim is for material uniformity, as a good particle size distribution (PSD) will deliver a better powder for compression or encapsulation. Importantly, this will also improve product solubility and bioavailability, ultimately delivering improved drug performance. At the same time, the selected milling method must be practicable for production, balancing all desirable attributes. In this regard, conical milling offers numerous benefits over alternative milling machines:

- Compared with oscillating mills, conical mills will achieve a similar PSD, but offer dramatically higher throughput on an equivalent size machine, faster to clean and re-assemble and give better durability.

- Compared with hammer mills, conical mills will produce less fines to give a tighter PSD, be easier to clean and reassemble, and will produce less heat, noise and dust (many hammer mills require dedicated extraction). It is particularly important to understand these benefits in order to select the right technology for a new process, or when looking to upgrade from an existing oscillating or hammer mill.

If your selection process determines the conical mill is the most suitable machine, there are many variables to experiment with. These include screen type, impeller type, impeller speed and material pressure on the screen. Indeed, there is significant work to undertake in the early lab stages, as screen specifications can become very detailed with variations in hole size, hole shape, plate thickness and open area - all of which will impact final particle size, shape and machine capacity.

There are usually three steps in the process: lab milling, pilot milling, and production milling. Although throughputs vary with each individual application, a plausible example of batches through scale-up would be 1-10 kgs in the lab, 25-100 kgs in the pilot plant and 400-800 kgs in production. Breaking it down in this way helps to remind us that scale-up is simply a methodical and staggered increase in milling throughput. The emphasis should be towards identifying and overcoming deviation between each stage, with the ultimate objective of manufacturing a high-quality and reproducible output, at the lowest possible cost.

Lab Milling

Lab milling is the discovery phase of product scale-up, providing R&D with a platform to test and study material behaviour during conical milling. This enables them to micro-monitor material properties (particle size distribution, particle shape) and identify process factors which impact or are impacted by the material (heat generation, capacity).

For example, a faster impeller speed will produce a smaller particle and higher throughput, but will also generate more heat. Many materials are temperature sensitive, so while pushing a particle to its limit may be suitable on a laboratory sized batch, in the context of production these limitations could prove debilitating. Similarly, a screen with a small hole will give a finer particle, but will also restrict capacity and generate more heat. Hence, a significant role of lab milling is to provide a balance between a desirable particle and a realistically achievable process - a key deliverable should be handing over critical process parameters for the larger-scale pilot and production mills to follow.

The target particle size distribution should be guided by the intended purpose of each ingredient and its contribution to the final product. To a large extent, the output of postmilled materials will depend on the degree of aggregation of the premilled ingredients. To give an accurate indication of eventual particle size distribution, it is recommended you plan to surrender a small material loss for each lab milling batch (approximately equivalent to a screen full of material). This should be regarded as a necessary evil; it is important to remember that the purpose of lab milling is to accurately forecast the outcome of a much larger production batch.

To be specific, at the end of a batch there is not enough downward gravitational force pushing material into the milling chamber. Consequently, although this material would eventually pass through the screen, the product would be 'stirring' rather than milling, taking an excessive amount of time, thereby producing a disproportionate amount of small particulate or fines.[1]

For example, on a lab size machine ~50g of a 1kg batch may be retained in the screen under these conditions (5%). Meanwhile, in production, only the last ~1kg of 600kgs would mill under the same conditions (0.166%). Hence, if both were left to mill the entirety of the batch, the lab machine would show a significantly larger proportion of fines and over-milled material than would be the reality in production.

It is obvious to note that the more rigorous and robust the small-scale work, the easier process scale-up will be. Lab milling results are used to draw correlations to proposed pilot and production milling setups, so should test all relevant variables and generate informative data sets. This is particularly pertinent for conical milling, where so many parameters can be changed on a single machine; hole size, hole shape, impeller type and impeller rotation speed. By probing the outcome of each variable, R&D staff can not only identify a path to production, but also gain an understanding of potential problems that could occur in a scale-up situation.

[1] Pressure from the weight of material on the screen might not seem relevant to average particle size and particle size distribution. However, the more pressure exerted on the screen, the less residence time of the material during milling. This results in less frequent impact by the impeller, minimising fines or over-milled particles.

Pressure is controlled by the feed rate and the feeder design; flood feeding of material exerts a constant pressure on the screen giving a tighter, more uniform PSD. This makes flood feeding the easiest to reproduce in scale-up, although it may not always be practicable and there may be justified reasoning to use discontinuous feeding. For example, if the material is prone to caking/blinding or if the feed rate from an upstream machine is not sufficient, a rotary valve or similar may be installed to control material flow.

Whatever process is ultimately designed must be workable in a real-world scenario, but it is important to remember that the more inconsistent the pressure on the screen, the more inconsistent the size and shape of the particle.

Pilot Milling

Pilot milling is a cautious step between lab milling and production milling. It is the stage that allows further investigation of your product and your process at an intermediate scale, before large amounts of money are committed to full-scale production. Equipment should aim to provide results that can be easily correlated to production lots, without requiring the significant outlay of funds for precious ingredients and capital equipment. Using scalable milling equipment, which has been tested via protocol in the lab with reference materials, will minimise experimentation and reduce the overall duration of the pilot phase.

The equipment used at this stage should subject the pharmaceutical material to additional stresses of different types and degrees than were present in the lab. The pilot plant should provide for environmental and process controls that were unlikely to be present in the laboratory. Since heat and humidity are so tightly tied to particle aggregation or dissociation, it is easy to see that machine parameters might need to be changed in the more controlled pilot environment. For example, if the room conditions such as temperature or humidity are different in the pilot plant to those in the laboratory, the material may behave differently (e.g. more or less aggregated, more or less prone to blinding). Consequently, a process change may be required to compensate, such as running at a lower / higher impeller speed or using a screen with smaller / larger holes to get closer to the original particle size distribution. Accordingly, room conditions from pilot to production should vary as little as possible. The same is true if trying to replicate a process between different geographical sites.

The raw ingredients used in scale-up should closely or exactly resemble those used in the previous stage of milling, or if unfeasible, then new ingredients need to be thoroughly tested and correlated with the original material. Ideally, new ingredients will be tested in the lab prior to introduction at the pilot or production plant. If there are large clumps in the bulk material that were absent in the laboratory testing (e.g. due to compaction in storage), then the resulting particle size distribution of milled material may differ. Should such variances occur, insight can be gained by studying patterns or parallels in the development, validation and batch reports.

Once all testing is complete, the pilot plant provides a final platform for R&D staff to intermingle with production staff before manufacture. It is an opportunity to transfer knowledge and concerns; this allows all groups to analyze and compare data, to give the required confidence that the process is comparable and scalable. At this stage, close liaison with the conical mill supplier is also recommended for drawing on process knowledge and understanding the capabilities and limitations of the machine prior to production commitments.

Production Milling

After completion of pilot testing, the required setup for production should now be clearly identified, with an accurate forecast of PSD and machine capacity. This is not to say that everything will work first time, but the majority of problems should already have been overcome and any outstanding issues should be solvable during the validation process (e.g. FAT, SAT, IQ, OQ, PQ).

Once all production parameters are agreed and fixed, three to five batches should be produced to prove consistency and alignment with anticipated performance. Assuming these are successful, then once the process is validated and the equipment is qualified, milling will become just another standard operating procedure at your facility.

To minimise the variability of this process and to ensure the hard-work undertaken in scale-up is not wasted, close control of machine operation is recommended. A good example may be the use of an HMI, which limits the operator to the simple execution of preset conditions, while affording the administrator a large degree of flexibility if required. This gives tighter control of functions such as speed; as learned in the laboratory impeller rotation speed can have a significant impact on particle size and heat generation. If the operator has control of machine speed, then a batch could be run on an incorrect setting (accidental or otherwise). Indeed, two operators may have differing ideas of 'what works best', regardless of approved procedure.

It is essential that the documented procedure is followed by technically qualified and adequately trained personnel. It is a process that will be integrated with the overall pharmaceutical production plan and be supported by Quality Control, Quality Assurance, Health Safety Environment and Engineering.

Attention should also be focused on a planned maintenance schedule, using milestones set in the Operation Manual for regular inspections and wear-part replacement. Furthermore, to prevent a production standstill, it is recommended that vital spare parts are kept in the maintenance department. Specifically, regularly used screens and impellers should be kept in stock for immediate replacement in case of loss, damage or wear.

Conclusion

It is perhaps unrealistic to expect that scale-up will occur without fine-tuning and that success in the lab will translate directly into success in production. Nonetheless, planning for scale-up should begin before lab studies have even commenced. The plan can then be adapted through each step, as more detailed information and knowledge is gained.

After each stage is complete, it is essential for the receiving team to study the batch record reports, in order to better understand the issues experienced in the development phase. It is also imperative that teams engage in cross-departmental communication, to ensure lessons learned are carried forward to maximise the chance of scale-up success.

By the time a product reaches production, a comprehensive and thorough scale-up will afford a high degree of confidence to be shared by the development and manufacturing teams, as well as outside regulators. From lab to pilot, and from pilot to production, a major deliverable should be to put forward specific recommendations with regard to the required combination of screen, impeller type and machine speed for achieving a repeatable process.

Overall, conical mills offer excellent scalability, producing predictable and comparable results as you progress towards larger batches. Following the above guidelines will smooth and accelerate this path; ultimately this helps to achieve the original objective of delivering the necessary product specification, while satisfying the requirements of a highly regulated production environment.

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