Pharmaceutical Granulation: An Established Technology in a Changing World

Optimizing the granulation process — the most important unit operation during the production of pharmaceutical oral solid dosage forms — is not only a critical aspect of operational excellence, it also plays a major role in preventing downstream compression problems.
A number of different granulation and compression technologies are available to pharmaceutical manufacturers, all of which have individual strengths and weaknesses depending on the specific application; however, to cite a popular online article: “The theory of granulation is often poorly understood and the selection of a particular machine and granulation method is frequently done on the basis of historical use and the operator’s own experience, rather than by using strict scientific or cost-benefit criteria.”

In most companies, the main driver behind choosing a granulation technique is tradition; if you visit a company A, it’s spray granulation; at company B, it’s high-shear granulation followed by fluid bed drying; the preferred technique at company C is roller compaction, etc. So, every organization has its preferred way of doing things.

Why granulate?
Very few people can actually assess whether a handful of granules are “good” or not, which means that the only way to test whether they’re fit-for-purpose is to run them through a production-scale tablet press to better understand their compression properties. Essentially, the granule is an intermediate that must possess certain characteristics that make it usable in a high-speed tablet press. As an example, weight is a critical quality attribute, which means that excellent flowability is paramount.

Another key issue is content variability. In a traditional batch operation, for example, you have several hundred kilos of material sitting above a tablet press. What with vacuum conveying or multi-floor layouts (which sometimes incorporate a drop of several meters), there is a significant risk of segregation. To minimize this, as opposed to simply working with a physical mixture of all the ingredients, you granulate to “freeze” the composition of the entire blend. In a nutshell, granules flow better and offer less risk of segregation.

A new approach
With large volume production, most companies aim to get their raw materials — especially excipients — as cost-effectively as possible, without necessarily paying too much attention to the physical form. Needle-shaped crystals and/or a wide particle distribution, etc. can be tolerated because the resulting mixture is combined with a binder and put into a high shear granulator. The process dynamics and mechanical energy produced during operation more often than not convert the powders into something that’s good enough to feed a tablet press.

The perennial problem during batch manufacturing was the risk of segregation. With a continuous process, however, operators are increasingly realizing that the major drawback of direct compression can be eliminated. It’s inherently possible to employ individual loss-in-weight (LiW) feeders for each ingredient and blend them inline in one or two stages — just prior to reaching the tablet press — removing the downtime between unit operations and drastically reducing the risk of segregation.

Although it may seem to be counterintuitive, it is more cost-efficient to spend more on higher quality raw materials and avoid the complexities (and hassle) of integrating a wet granulation stage. In conclusion, this route to market is also faster because, during development, there are only two separate unit operations — blending and compression — to optimize. And, furthermore, the process generally involves less API and more easily accommodates the concept of operational excellence.

Conclusion
Poorly granulated materials will not compress well and most fine pharmaceutical compounds require granulation to improve their flowability and processing properties prior to tableting. With process optimization in mind, critical decisions need to made early on during development. This is when collaboration is key to ensuring that when a formulation reaches commercial-stage production, industrial-scale machines are actually capable of reaching the output values they’ve been designed to achieve, problem free. Poor mixing, granulating and drying will lead to issues with tableting that cannot be rectified by adjusting the press.

References

Further reading
www.in-pharmatechnologist.com/Article/2015/05/01/FDA-calls-on-manufacturers-to-begin-switch-from-batch-to-continuous-production

For more information
Dr Harald Stahl
Head of Innovation and Strategy
GEA Group
www.gea.com/pharma