

Option 1 – Pressure’s On: How Roller Compaction is Helping Pharma’s Formulators Achieve Better Poorly Soluble API Delivery

Advances in combinatorial chemistry and high-throughput screening continue to introduce poorly water-soluble active ingredient (API) chemistries into pharmaceutical development. For more than 25 years, high-throughput chemistries and techniques have driven a dramatic increase in the number of poorly water-soluble drug candidates in development. Because these methodologies have become so well-understood, pharmacologists are now better able to successfully synthesize more potential candidate compounds and efficiently optimise drug-receptor binding to achieve better selectivity.

Approximately 40% of drugs with market approval and nearly 90% of molecules in the discovery pipeline are poorly water-soluble.¹ Issues associated with poor solubility can lead to low bioavailability and result in suboptimal drug delivery. For those reasons and more, the majority of new drug development failures have been attributed to poor water solubility. Although the risk remains that APIs can fail in development because bioavailability issues can’t be overcome, pharma and its contract partners have become extremely good at applying enabling technologies that in final dose form overcome the pharmacokinetic conflicts of even the “poorest” poorly soluble API chemistries.

Amorphous Forms and Solid Dispersions Required

Stable crystal drugs chemistries often present solubilisation issues due to high lattice energy. Typically, to achieve desired endpoints more hydrophobic domains are ‘bolted’ to the molecular scaffold which can increase molecular weight and hydrophobicity. Both of these attributes contribute to reduced aqueous solubility.¹

Pharma’s experience has proven disordered amorphous solid dispersion (ASD) particle forms offer distinct advantages over crystal forms relative to solubility. Hence, changing the solid-state characteristics of the API can help render the molecule more water-soluble. The advent of new techniques

to improve stability of amorphous forms will continue to support the challenges of formulating and processing poorly soluble chemistries into successful commercial products ready to meet patient needs more effectively.

Enabling Technologies

Granulation, the technique of particle enlargement by agglomeration, is recognised as one of the best ways to manage the pharmacokinetic dynamics of poorly soluble APIs and formulate them for use in OSDs¹. During the process, small, fine or coarse particles are converted into larger agglomerates otherwise known as granules.

This transforms fine powders into free-flowing, dust-free granules that are easy to compress into tablets or fill into capsules precisely.

Generally, the granulation step occurs after initial dry mixing of the necessary powder ingredients and API so that a homogeneous distribution of each ingredient throughout the mixture is accomplished. Because most particles encountered in OSD formulations are in the range of 0.2 to 4.0 mm, they are generally produced in an intermediary size (ranging from 0.2 to 0.5 mm) first, ready to be either packed as a finished dose form or be mixed with other excipients before tablet compaction or capsule filling.

Wet versus dry granulation? It’s up to the chemistry

Granulation can be divided into two ‘types’: wet granulation that utilises a liquid in the process and dry granulation which does not. Selection requires thorough knowledge of physicochemical properties of the drug, excipients involved, required flow and release properties, to name just a few of the critical aspects of the drug substance.²

Dry granulation is the go-to manufacturing process for ASD-enabled poorly soluble APIs and intermediates for two primary reasons:

1. Process avoids the addition of water, important in maintaining the amorphous form of the API formed via enabling technologies

2. Provides densification needed for the enabled intermediate where the drug load in the intermediate can typically range between 10–50%

The inherently poor flow properties of most small molecule APIs, the worsening of flow associated with particle size reduction techniques such as micronisation or nanonisation and the low drug loads associated with HPAPIs make granulation almost necessary for facile downstream processing of oral solid dosage forms.

Granulation’s “enabling” technologies include roller compaction, spray drying, supercritical fluid, low/high shear mixing, fluid bed granulation, extrusion/spheronisation. However well understood, granulation presents many challenges due to quality requirements associated with content uniformity and physicochemical properties. These include granule size, bulk density, porosity, hardness, moisture, compressibility, as well as with physical and chemical stability of the drug.

Roller Compaction to the Rescue

Dry granulation agglomerates powder ingredients without the use of liquid binders or water. When granulated, the crystalline chemistries of poorly soluble APIs become more soluble and bioavailable. However, when the granules are exposed to water, it can cause them to recrystallise and reverse the solubility gains from granulating the ASDs in the first place.

Roller compaction is one method of producing granulates without moisture because it uses pressure to minimise the space between individual particles. In essence it’s a densification process that has proven to be extremely effective at managing the inherent properties of the “brick dust” powders poorly soluble APIs often present to manufacturers and formulators. As opposed to wet granulation, dry granulation via roller compaction is a truly continuous-flow process that offers manufacturers various economies and advantages operationally.

Dry granulation systems require lower capital investment in facilities or equipment. This, together with much lower maintenance



processing associated with the use of less energy, labour and time. Roller compaction being a continuous process makes scale-up that much easier and a function solely of time. The ability to automate the process with recipes also adds to the efficiency of scale-up.

Central to the process is the machine. Central to the capabilities of the machine are pharma's equipment suppliers. Ostensibly modular, current systems in service offer great utility in delivering the process efficiently. Functionally, today's roller compactors can be calibrated with precision to assure the formulation's ingredients achieve required properties. Equipment suppliers have also seen continuous operational improvements and innovation to overcome the tough granulation challenges poorly soluble compounds present.

However, from the first "mile" of ribbon to the last, delivering the stable, compliant validatable process developers need to assure critical quality attributes is up to the operators – not to mention the formulation and analytical teams assigned to the program. However, these capabilities are accessed, in-house or with external manufacturing partners, the more experience with dry granulation and roller compaction the more likely all stakeholders will yield better results for all stakeholders, especially patients.

requirements results in drastically reduced lifecycle costs. Currently, the throughput of common dry granulation systems can reach approximately 400kg/h.

Benefits of Roller Compaction

Compared to wet granulation and other dry granulation methods, roller compaction offers advantages that make it more suitable for use in pharmaceutical production applications, such as:

- **Primarily addresses the poor flowability of powders** and other issues, such as dustiness, low bulk density and propensity for segregation.
- **Better suitability for heat and moisture-sensitive compounds in ASD forms.** Dry granulation allows for granulation without liquids, so it is ideal for APIs that are degraded by the presence of moisture or heat. Since no liquids are added, there is no need for a drying stage, which is ideal, especially for the processing of materials with low melting or thermal degradation points.

- **Greater process accuracy.** Compared to slugging, roller compacted ingredients deliver more consistent powder flow, which results in more consistent compaction results.
- **Easier scalability.** For roller compaction operations, both pilot and commercial product batches can occur on the same machine, making it simple to expand production without additional machinery investment.
- **Lower operational costs.** Since the roller compaction process eliminates the need for material wetting and drying stages, operational costs are reduced compared to wet granulation operations.

Quality Depends on Equipment, Supplier and the People Applying it

Roller compaction offers a straightforward, seamlessly scalable granulation technique to increase particle size while also improving blend uniformity of low dose APIs. Dry granulation has supplanted wet granulation techniques for the overall efficiency in

REFERENCES

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4629443/>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4401168/>



Anshul Gupta

Anshul is responsible for technical and scientific oversight of client projects. He works across various functional teams in RFP considerations and scope of work development, proposal delivery, client and prospective client meetings, and contributes to the company's thought leadership agenda. Anshul holds a Bachelor of Pharmacy from the RGPV University, Bhopal, India, a Master of Science in Pharmaceutical Sciences from Temple University, and a Doctorate in Pharmaceutical Sciences from the University of Kentucky. He holds the RAC credential.