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White Paper

Application of Dry Granulation to Facilitate Raw Material Handling

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Pharmaceutical and biopharmaceutical manufacturing relies on the timely and seamless orchestration of many steps to meet aggressive timelines and ensure operational efficiency. A fundamental element of the processing workflow that can impact schedules is the use of multi-ton quantities of bulk raw materials such as buffers, salts and stabilizing chemicals. These raw materials are typically prepared in a just-in-time manner to meet dynamic production needs and enable rapid changeovers.

Handling bulk powders can be especially challenging at a large scale as weighing and dispensing steps are time- and labor-intensive and the likelihood of dust formation puts operators at risk. In addition, raw materials such as potassium chloride, glycine and urea naturally tend to cake and can even completely solidify, especially when in long-term storage. An added difficulty is the fact that the amount of caking in a bulk container is hard to predict as it depends on transport and storage conditions; this unknown can lead to unexpected process delays and interruptions.

Caking of chemicals increases operational and safety risks as a manual de-caking process is often being employed to prepare the raw materials. Manual de-caking of solid blocks of bulk powders, sometimes performed using a hammer, wastes valuable time and poses a risk of serious injury to the operator. Caking can also result in quality deviations, increase the risk of contamination, and escalate operational costs due to several factors including:

- The loss of time needed to break apart solidified blocks
- Difficulty in sampling and weighing the caked materials
- An inability to completely empty the primary packaging

A variety of approaches have been used to avoid caking, such as minimizing material storage time and ordering smaller packaging sizes. Unfortunately, such approaches do not prevent the caking process and may not be compatible with just-in-time manufacturing processes. They may simply lead to other production challenges and even create process interruptions. Given the impact that caking of bulk chemicals can have on the manufacturing workflow, an alternative solution is clearly needed to ensure that handling of raw materials align with manufacturing imperatives and business drivers of speed, quality, flexibility and cost.

Solving the Caking Problem with Granulation

Chemical raw material caking can be addressed using a process known as granulation. Compared to bulk powders, granulated materials have better flowability and are easier to handle, with far less caking, even after long-term storage. Any small clumps that may occasionally emerge can usually be easily reduced in size. With these properties, granules offer better processability, accelerate manufacturing processes and improve operator safety.

Wet and dry granulation processes are used in the pharmaceutical workflow, most commonly for excipients and the production of solid dosage forms (Figure 1). The wet granulation process uses a liquid binder/solvent to facilitate agglomeration of dry powder particles while dry granulation incorporates mechanical compression either by slugging, or roller compaction. Because dry granulation does not require a liquid binder, it is preferred for compaction of chemical raw materials as there is no risk in alterations to the chemical composition.

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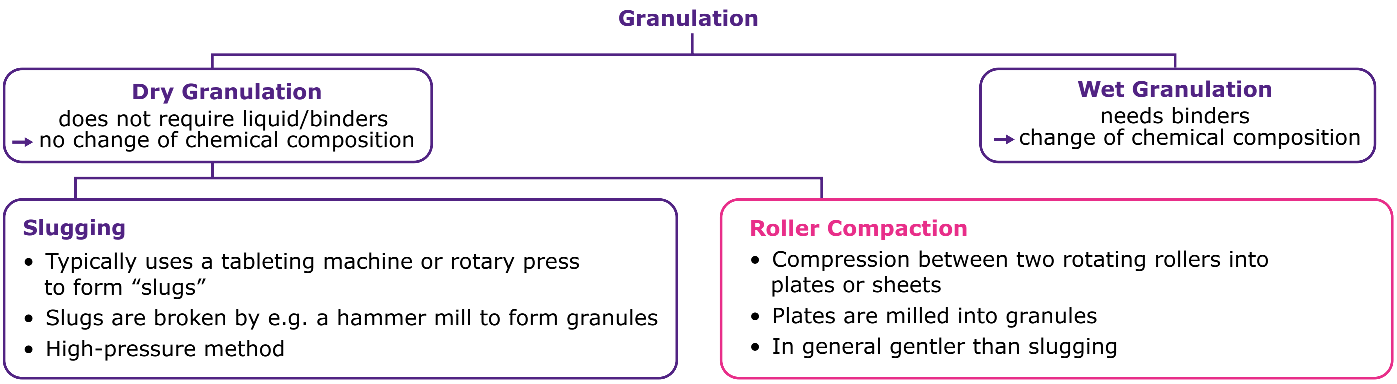


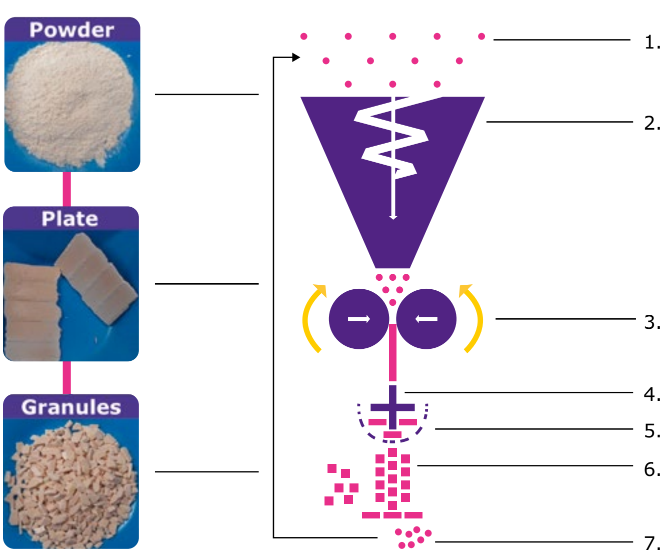
Figure 1.

Comparison of granulation techniques.

With slugging, tableting machines or rotary presses are used to form slugs which are then broken by a hammer mill to form granules. In roller compaction, the raw material is compressed into plates or sheets between two rotating rollers, which are then milled into granules. Compared to slugging, roller compaction is very gentle, making it the preferred approach with heat- and moisture-sensitive raw materials.[1–3]

Dry Granulation by Roller Compaction

Figure 2 provides a schematic view of dry granulation using roller compaction. The bulk material to be granulated is first put into a funnel which has a mixer and tamp auger for transporting the material toward the rotating rollers. Hydraulic compression is then applied to form the plates. Because the use of a high pressure can lead to an increase in temperature, the rollers are temperature-controlled to protect raw materials. The plates are pressed together and transported to the rotor sieve mill which produces the final granules at the desired size. Fine particles that fall below the desired size can increase the probability of re-caking and are recirculated to the funnel for a second round of granulation, thus minimizing product loss.



To produce high quality particles of a consistent size using dry granulation by roller compaction several key process parameters must be considered:

- Pressure is the main parameter which determines the hardness and integrity of the granules. While there is an upper limit, higher pressures usually result in harder granules.
- Roller speed determines the retention time of the material under pressure. A faster speed results in higher throughput but the material is compressed for a shorter period. In contrast, slower rotating rollers lead to a lower throughput, but the material is more condensed.
- The interspace between the two rollers influences the pressure applied to the material. The smaller the interspace, the more the material is pressed together. This parameter is fixed during the process and must be aligned with the feeding speed; for more material to pass through the rollers, the interspace must be sufficiently large.
- The size of the sieve mesh used during milling is the main parameter influencing particle size distribution.
- The chemical characteristics of the raw material including crystallinity, plasticity, age and melting point help determine suitability for dry granulation by roller compaction. If the raw material is not suitable for this approach, there may be limited cohesion and no granules would be formed.

Figure 2.

Principle of dry granulation by roller compaction. A typical roller compactor setup comprises (1) bulk material, (2) funnel with mixer and tamp auger, (3) hydraulic compression rolls (temperature controlled), (4) rotor sieve mill, (5) vibrating sieve, (6) final granules, (7) fine particles re-circulation.

Characteristics of Granulated Raw Materials

The dry granulation process using roller compaction confers several characteristics on chemical raw materials that deliver important advantages to the manufacturing workflow.

Particle Size Distribution

Particle size resulting from dry granulation is always a distribution and is influenced by the size of the milling sieve and the material itself. Figure 3A shows the size distribution of urea particles of approximately 1–6 mm following dry granulation with roller compaction using a milling sieve size of 6 mm and a vibrating sieving tower with sieve sizes 500, 1,000, 2,000, 2,800 and 4,000 µm. The weight fraction was recorded after 10, 20 and 30 min and the mass-% of all fractions was determined.

Importantly, there was a very low portion of fine particles (<1 mm). Such fine particles should be minimized as they can influence re-caking behavior and interfere with flowability of the material. As described above, this can be achieved by recirculating fines back into the funnel for a second granulation.

Particle Appearance

Figure 3B and C show the appearance of granulated urea (B) and potassium chloride (C) following a 12-month stability study at 25 °C and 60% relative humidity. The non-granulated bulk materials are shown in the bottom rows of each panel and experienced a high percentage of solidified blocks that were difficult to break apart (68% for urea and 42% for potassium chloride). The granulated urea and potassium chloride had significantly less caking (12% and 0% clumping, respectively) after 12 months in storage compared to the bulk material. In contrast to the bulk powder, the clumps of granulated urea were easy to break apart.

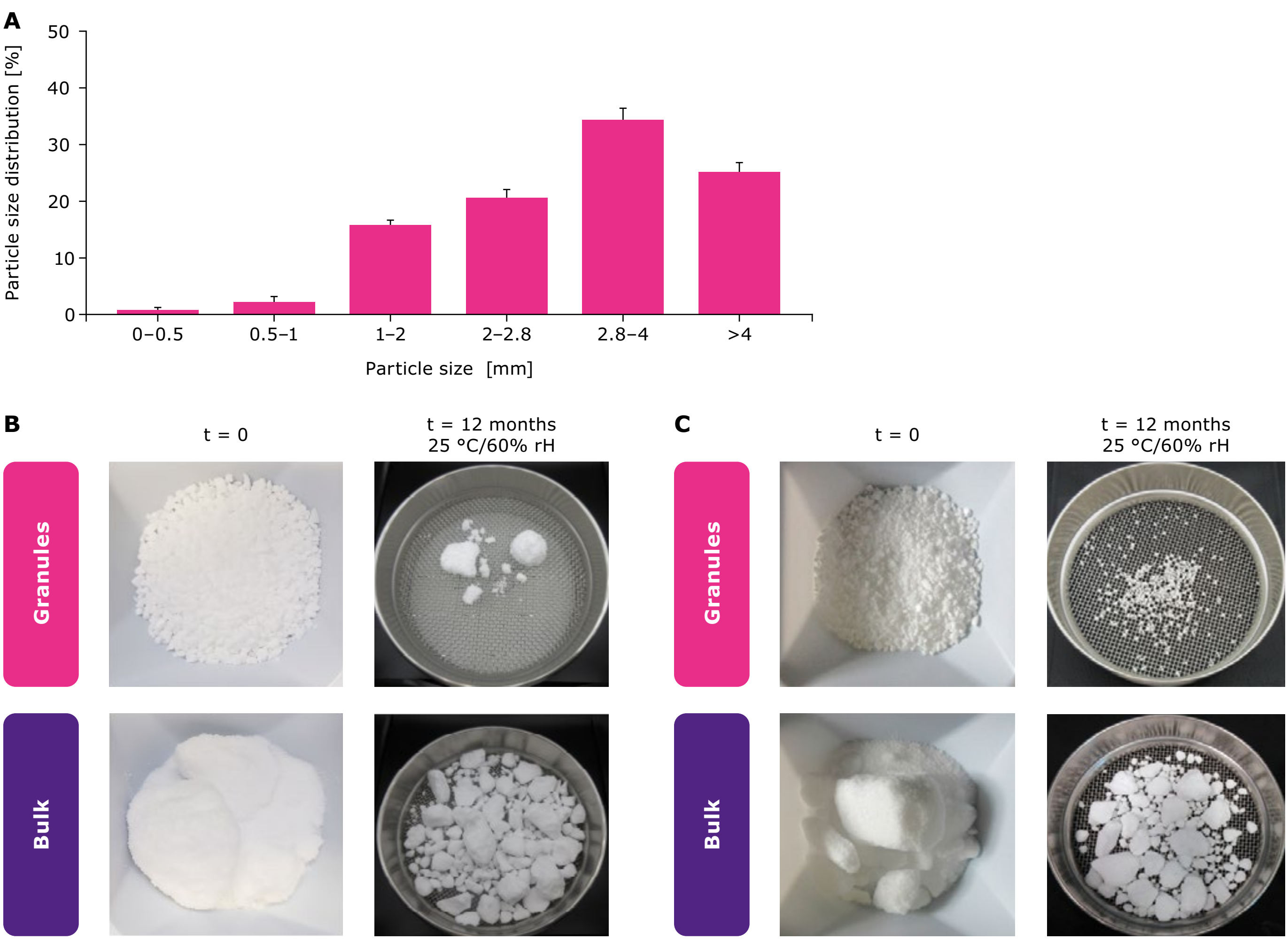


Figure 3.

Material characteristics after dry granulation using roller compaction: A) urea particle size distribution, B) appearance of granulated urea following a 12-month stability study and C) appearance of potassium chloride following a 12-month stability study.

Flowability

Granulation is commonly applied to improve flowability of powders which facilitates handling and processability of the raw materials. To compare flowability of bulk powder and granulated materials in this specific case, a powder analyzer was used. The material is placed on a rotating plate whose angle is then increased; the avalanche angle is that at which material starts to flow down the plate and ranges from non-satisfactory to excellent flowability. A lower avalanche angle indicates better flowability while a higher angle indicates reduced flowability. As shown in Figure 4, granulated raw materials showed strongly improved flowability compared to bulk material. Moreover, flowability of all granulated materials tested was almost equal, which provides improved handling in processes comprising different kinds of chemicals.

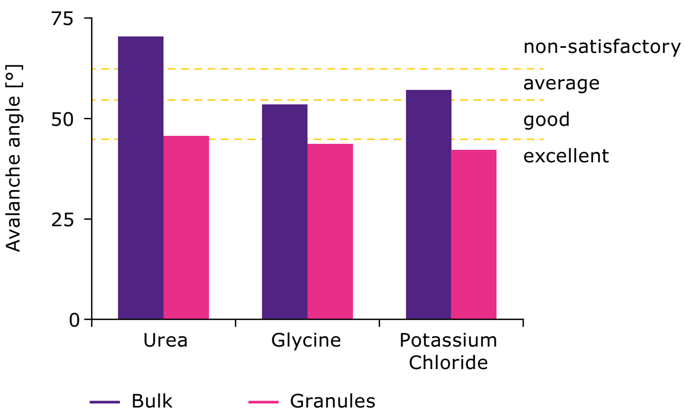


Figure 4.

Comparison of flowability of granulated and bulk raw materials. Flowability was determined based on the avalanche angle as measured using a powder analyzer: <45° excellent; 45–55° good; 55–62.5° average; >62.5° non-satisfactory.

Mechanical Stability

The mechanical stability of granulated particles was evaluated under simulated stress conditions using a friability tester to determine the risk of crushing during transport, handling, and storage. Granules were placed in an abrasion drum with heavy ceramic balls and the mass percentage of fine particles generated was compared to the overall mass to determine the percentage of abrasion. Abrasion of the granulated materials varied based on the respective chemical but was always less than 4%, indicating excellent integrity (Figure 5).

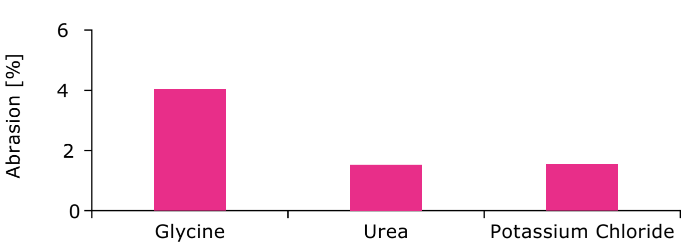


Figure 5.

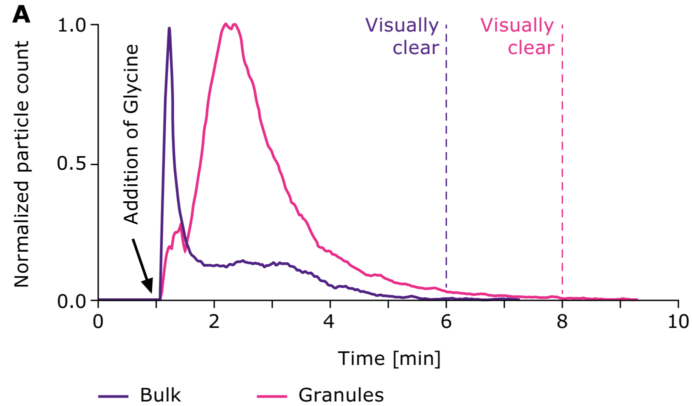
Abrasion of granulated materials under simulated mechanical stress conditions using a friability tester.

Dissolution Behavior

Dissolution behavior of chemical raw materials is especially important, as manufacturing processes typically require both fast and complete dissolution. To determine the behavior of granulated and non-granulated material, the kinetics of dissolution were measured with focused beam reflectance measurement (FBRM). In this method, a laser beam detects and counts particles within the solution.

Dissolution behavior of the glycine and potassium chloride granulated material was comparable to the bulk material while the granulated urea, with a lower surface area than the bulk powder, required a slightly longer time (Figure 6). Even with a slower dissolution, the overall time savings as compared to caked bulk materials are evident as manual de-caking, sampling and weighing are eliminated.

A



B

	Urea	Glycine	Potassium Chloride
Bulk	5.0 min	6.0 min	6.0 min
Granules	8.5 min	8.0 min	6.5 min

Figure 6.

(A) Dissolution kinetics of glycine in granulated and bulk powder form as measured with FBRM. (B) Time until complete dissolution for urea, glycine and potassium chloride in granulated and bulk powder form.

Conclusion

The presented results demonstrate that granulated raw materials offer distinct advantages over raw materials in their non-granulated, powder bulk form. Regarding processability and performance, granulated materials outperform bulk material in many aspects. Long-term stability studies confirmed strongly reduced tendency for caking. In addition, flowability was strongly improved and dissolution behavior was comparable. Moreover, granules were shown to have excellent integrity even under harsh mechanical stress. As the need for manual de-caking becomes obsolete or at least strongly reduced, operator safety can be significantly improved.

Overall, granulated chemical raw materials offer important benefits to the pharmaceutical and biopharmaceutical manufacturing process. By significantly reducing the tendency of bulk materials to cake, flowability and processability are improved, enabling accelerated workflows, just-in-time production and increased operator safety.

Granulated Product Portfolio

Urea, glycine, and potassium chloride are available in granulated form in our Emprove® Expert grade with low endotoxin levels, making them well suitable for high-risk applications. These granulated raw materials are multi-compendial and compliant with major pharmacopoeias. They are available in different pack sizes and three different batches for qualification purposes. The Emprove® Program provides the documentation needed to meet the latest regulatory requirements for risk assessment and facilitates development of more robust processes. Documentation is provided in the form of three dossiers: material qualification, quality management and operational excellence.

For more information on our granulated product portfolio, please visit sigmaaldrich.com/granulated-materials.

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