Addressing Handling Challenges of Chemicals by Dry Granulation

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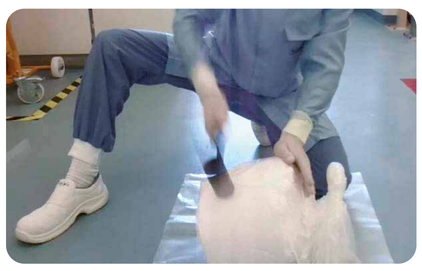
Introduction

Buffers, salts and stabilizing chemicals are used in multi-ton quantities during biopharmaceutical manufacturing. The handling of such quantities in a pharmaceutical production environment can be challenging: Caking and clumping of chemicals, dust formation and laborious weighing have a negative impact on manufacturing efficiency and may even lead to process interruptions, quality deviations and operator safety risks.



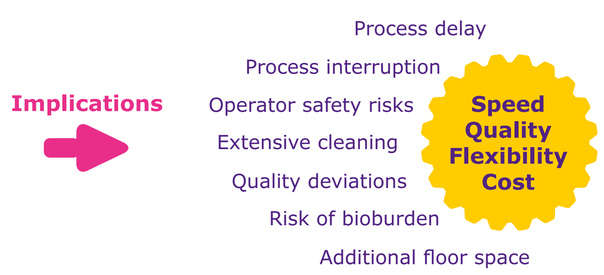


Figure 1: Potential effects of poor material characteristics.

Dry granulation was assessed as a potential means to overcome caking issues and improve handling. As it uses compression force only without water or other additives, it is ideal for highly sensitive materials and offers the benefit of ensuring that characteristics of the raw materials are preserved.

Materials and Methods

Bulk powders were dry-granulated as shown in Figure 2 using an RC120 roller compactor (Powtec GmbH, Remscheid, Germany). To assess the potential of dry granulation to reduce caking, flowability and dissolution kinetics of granulated glycine and urea were compared to the respective bulk material before and after storage at ambient (25 °C / 60 % rH) and accelerated conditions (40 °C / 75 % rH). At specified time points the bottles were inverted and the material was sieved to assess the extent of clumping. Flowability of material after storage was assessed via measurement of the avalanche angle using a Revolution Powder Analyzer (PS Prozesstechnik, Basel, Switzerland). Dissolution studies were performed by dissolving 80 g of the respective material in 800 mL of purified water. Samples were stirred in a 1.2 L bioreactor with Rushton impellors at 250 rpm and at room temperature. Undissolved particles were determined by focused beam reflectance measurement and visual inspection. Material integrity was tested using an abrasion drum with added ceramic balls. The drum was rotated at 20 rpm for 10 min and the percentage of fine particles mass <500 µm was determined.

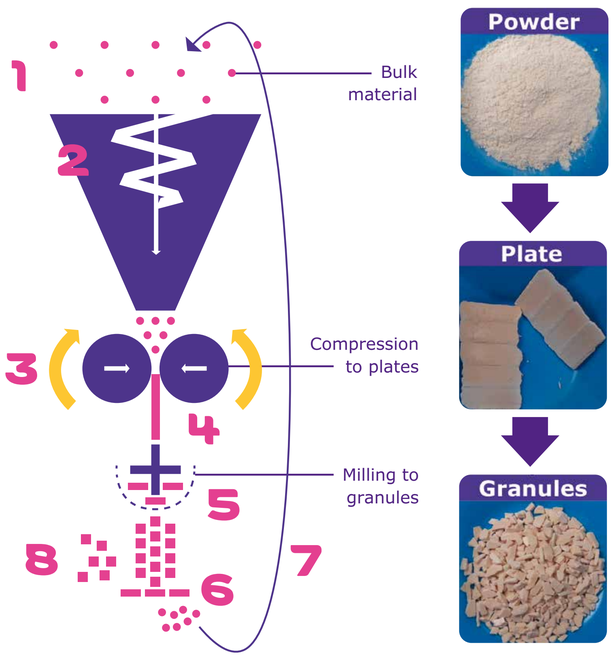


Figure 2:
Schematic depiction of dry-granulation process. The powder is filled in the funnel (1), conveyed to the rolls by a mixer and tamp auger (2), and compressed between temperature-controlled rolls using hydraulic pressure (3). The resulting plate (4) is milled to granules using a rotor sieve mill (5). A vibrating sieve separates non-compacted fines from granules (6) which are then recirculated back into the funnel to increase final yield (7). Final granules are collected (8).

Results

Stability Studies and Caking Behavior

After 7 weeks under accelerated conditions at 40 °C / 75 % rH, granulated materials showed significantly less caking compared to the "standard" bulk material (powder): The bulk material needed de-caking efforts to be removed from the container while granules were still free-flowing and could be poured out easily (Figure 3). The same effect was observed during long-term stability studies at ambient conditions (25 °C / 60 % rH). Here granulated material showed significantly less clumping compared to bulk material (Figure 4).

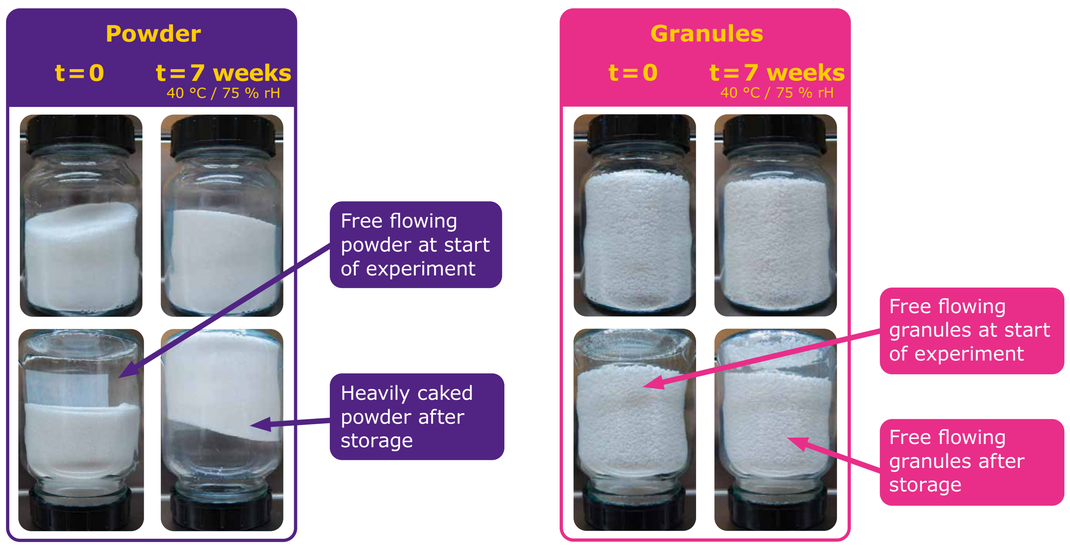
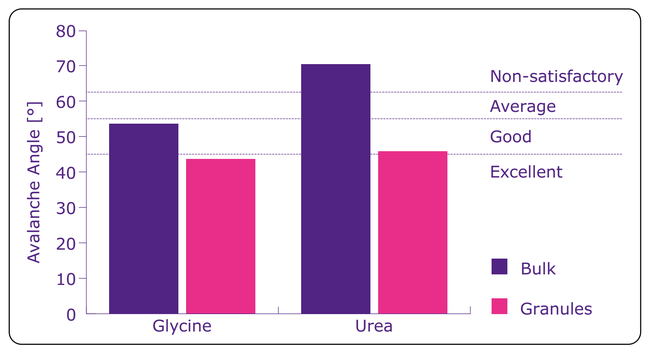


Figure 3: Comparison of caking behavior of bulk and granulated material before and after storage under accelerated conditions: **example glycine.**

Figure 4: Comparison of caking behavior of bulk and granulated material before and after storage under ambient conditions: **example urea.**

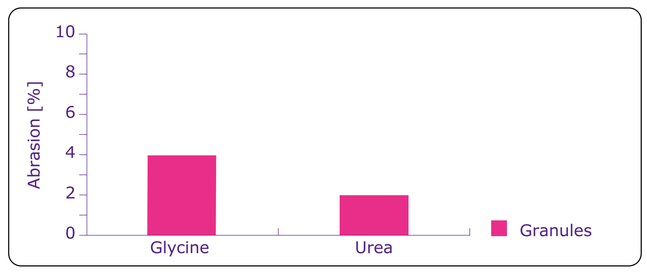
Flowability



Flowability measurements revealed an improvement of flowability of the granules in comparison to bulk materials. An improvement from non-satisfactory to good and from good to excellent was observed for granulated urea and granulated glycine, respectively.

Figure 5: Comparison of material flowability.

Mechanical Stability



Sustained integrity of granules during transport and storage is key to preserve the material's positive characteristics. Abrasion tests confirmed an excellent integrity for both granulated glycine and urea with abrasion rates of only 3.8 % and 1.8 %, respectively.

Figure 6: Abrasion rates of granulated glycine and granulated urea.

Dissolution

Dissolution experiments showed slightly prolonged dissolution times for granules compared to bulk material. However, if de-caking steps for the bulk material are taken into consideration (>1 h for larger volumes), overall process time is improved for granulated material despite the observed difference in dissolution time.

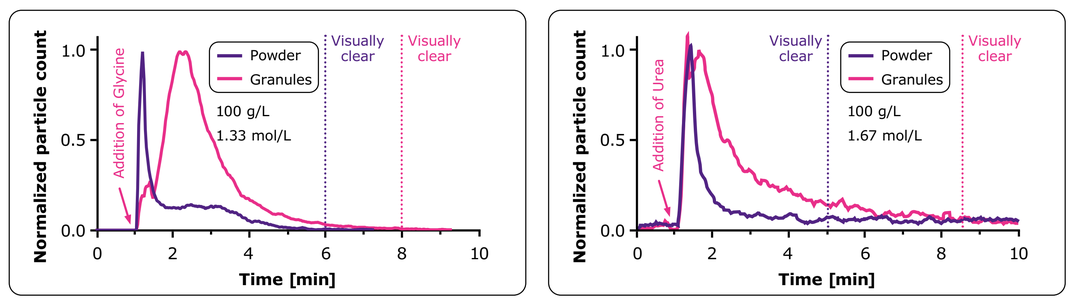


Figure 7: Comparison of dissolution behavior of bulk and granulated material showing results for glycine (left) and urea (right).

Summary

Dry granulation of raw materials such as urea and glycine resulted in greatly reduced caking, even under accelerated storage conditions. In addition, the granules showed good mechanical stability and improved flowability as compared to bulk material. Although the dissolution kinetics of granules can be slightly longer, their better handling characteristics more than outweigh the additional time needed for dissolution.

In summary, granulated raw materials show great promise to facilitate processability, avoid disruptions and speed up handling in a manufacturing environment while at the same time increasing the safety of operators.

Granulated Merck Products

Raw materials currently commercially available in granulated form:

Product Name	Art. Number
Ammonium Sulfate Granulated EMPROVE® EXPERT ACS, ChP, NF	104161
Glycine Granulated EMPROVE® EXPERT Ph Eur, BP, ChP, JP, USP	103669
Potassium Chloride Granulated EMPROVE® EXPERT Ph Eur, BP, JP, USP	104165
Sodium Chloride Granulated EMPROVE® EXPERT Ph Eur, BP, JP, USP	104163
Urea Granulated EMPROVE® EXPERT Ph Eur, BP, JP, USP, ACS	104166

Diverse pack sizes available. Additional products are currently under development.

Lit. No. MK_PS6722EN 08/2022

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