GO WITH THE FLOW – SOLVING POWDER FLOW CHALLENGES BEFORE PRODUCTION

In this article, Jonathan Gaik, Director, Natoli Scientific, discusses the various problems in tablet compression that can be caused by not giving due care to powder flow in the development stage and how, by doing so, what would be serious problems at the industrial scale can be solved in advance.

Ideally, an API powder will be one that flows well, is stable, self-lubricates, compacts well and is not strain-rate sensitive. While all the listed properties are important, the one that is truly critical is powder flow; most challenges in the tableting process begin with, or can be traced back to, flow. In the formulation development process, excipients such as glidants, binders and lubricants are added to the API to improve its flowability.

Challenges originating in the flowability of powders become more apparent when scaling up to full production. A seemingly minor product fault during R&D can become an unmanageable nightmare when scaled up to industrial production, by which point making changes to a formulation is costly and time-consuming. Conducting studies on a formulation during R&D and scale-up can help identify and solve potential powder-flow issues before moving into commercial production.

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STORAGE CONDITIONS

Humidity levels within storage or production areas can affect a powder's properties and thus how it flows. Additional moisture can increase a powder's potential to form hydrogen bonds that may cause a more cohesive powder that will restrict flow. Hold-time studies during R&D – establishing the time limits of holding a formulation at different stages of production – are crucial to determining the effects of storage conditions on the formulation. Maintaining an environmentally controlled storage and production area is vital to a formulation's flow characteristics.

BLENDING

Flow difficulties at the blending step often manifest as slow/no discharge or ratholing. The most common causes of these issues are:

- Improper storage
- Poorly selected binder that is too cohesive with the API
- Lack of glidant
- Improper order of addition
- Incorrect blending procedure.

The best way to establish flowability is to compare flow on a Flodex™ powder flow tester (Teledyne Hanson Research, CA, US) with the tablet configuration to determine whether the powder's intrinsic flow is close or equivalent to the cross-section of the tablet press die. For example, testing on a Flodex™ may show that a neat API powder has flowability of 26 mm, with a round tablet design of 12 mm in diameter. In such a case, the formulator would

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Jonathan Gaik
Director
T: +1 636 926 8900
E: jgaik@natoli.com

Natoli Engineering Company Inc
28 Research Park Circle
St Charles, MO 63304
United States

www.natoli.com/natoli-scientific/

need to re-examine the concentration and types of glidants and binders to achieve a target intrinsic flowability of 12 mm or less. Once that has been achieved, lubricants can be added and evaluated for flow.

Material interactions will guide the order of excipient addition and blending procedures. For example, if a glidant is needed, consider a pre-blend step to maximise the interaction between the glidant and the poorly flowing materials. A pre-blend step usually lasts between two to eight minutes. The optimum length of time can be determined using a Flodex™. Blend uniformity (BU) studies ensure APIs are adequately blended with excipients. BU studies can give formulators clear evidence of whether or not a formulation is within specification before moving to the next step in the process.

HOPPER DESIGN AND POWDER SEGREGATION

After blending, the powder is discharged to the hopper, where the formulator must ensure the powder's flow properties are adequate for it to successfully enter the gravity or force feeder. Difficulties when discharging a powder blend, including erratic flow, no flow and segregation, can be due to improper hopper design. Studies are conducted in R&D to calculate measurements like angle of repose and wall friction based on the powder properties. This information can be used to design the hopper's shape and determine the best material of construction and surface finish for encouraging powder flow.

Powder segregation within the hopper may result from formulation design or improper transfer. One type of segregation, called sifting, occurs when gravity or tablet press vibrations cause larger particles to separate from the smaller particles. Smaller particles filter to the bottom while the larger particles rise to the top (Figure 1). Particle size distribution and density of all materials within the powder blend are key considerations to prevent sifting segregation. Researchers can conduct studies according to ASTM International standards to help understand whether segregation is occurring and by what mechanism.

Segregation happening at this point in the process can affect tablet quality, possibly causing capping, lamination and/or high ejection forces. Conducting content uniformity (CU) studies can help determine

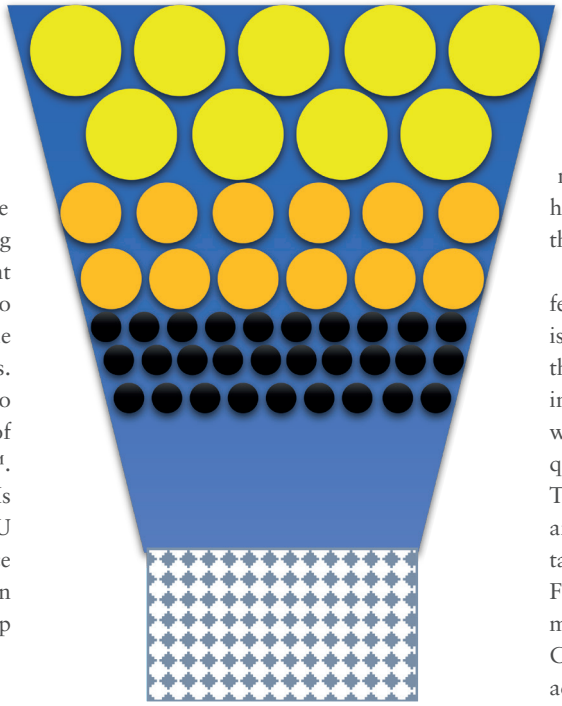

Figure 1: Particle size and density variation within a hopper under sifting.

whether the batch is consistent and within specification. CU studies should follow the guidelines set forth by the US FDA under 21 CFR 211.110.

TABLET PRESS CONSIDERATIONS

Flow challenges on the tablet press can cause tablet quality issues such as weight variability, content uniformity and/or tablet defects.

Weight variability can be driven by a poorly flowing powder or agglomeration by a material within the powder. Each die in the tablet press sits under the opening in the feed frame for only a small amount of time, usually milliseconds. Therefore, the flow rate must be calculated and tested to ensure that the powder flow can keep pace with the feeder and turret speed, thus adequately filling the dies to the correct weight. Agglomeration might not be detected in flowability studies, however it can become a localised flow event that randomly causes weight variability.

Additionally, matching the turret and feeder speed to the flow rate of the powder is necessary to prevent over-blending in the feed frame. Over-blending can result in segregation or excessive lubrication, which can, in turn, lead to poor tablet quality in terms of CU or compactibility. To identify these issues, CU samples are typically collected in set intervals as tablets are produced on the tablet press. Figure 2 shows an example CU assay at 15 minute intervals during tablet production. CU1 shows tablets that are within the acceptable content uniformity range, CU2 shows an example of sifting segregation and CU3 shows irregular, non-uniform tablet content due to over-blending. CU samples can help identify specific problems based on the results, however, unless they are paired with BU studies, they

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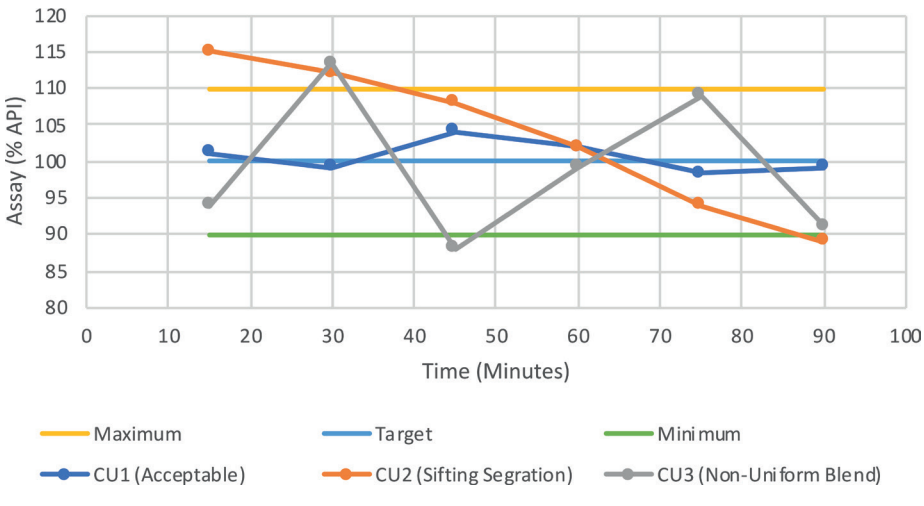

Figure 2: Tablet content uniformity assay studies.

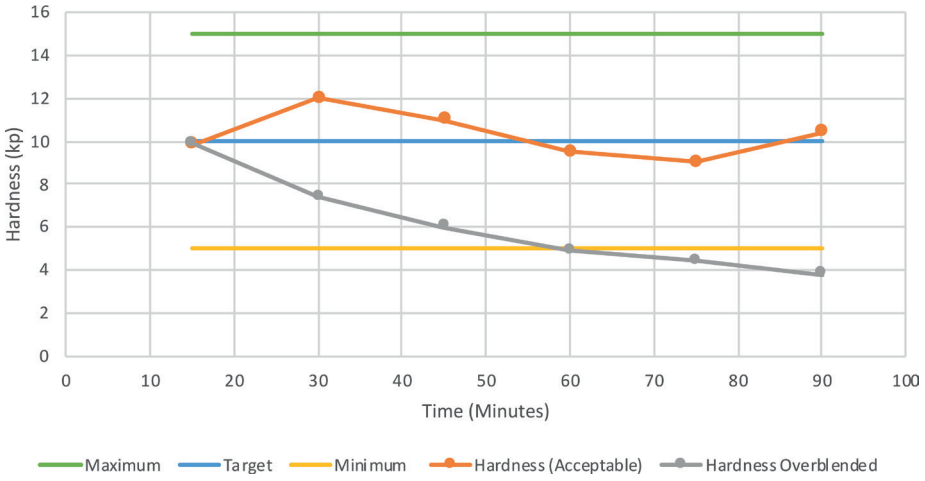

Figure 3: Tablet content uniformity hardness studies.

will not be able to isolate where the issue is occurring. Changes in hardness can be identified with the same CU studies. See Figure 3 for CU tablet hardness study.

Finally, poor powder flow can result in tablet defects, such as sticking and picking, which may be caused by entrapped air within the tablet press die. Formulation design, engraving, tooling material or coating can improve powder flow during the compression cycle and thus reduce tablet defects. Gentle curvature in engraving cuts results in more laminar and less turbulent powder flow. Tooling material and metal coatings should be selected to decrease the coefficient of friction while increasing release characteristics, which will also improve powder flow.

ENSURING GOOD POWDER FLOW

A poorly flowing powder can affect tablet quality at every step in the process. Key factors to consider when encountering a powder that doesn't flow well are:

- Formulation design
- Storage conditions
- Tablet design
- Mechanical design of processing equipment.

Powder rheology studies, such as shear strength and wall friction, which can be conducted on an FT4 Powder Rheometer® (Freeman Technology, UK), alongside flowability studies on a Flodex™, can be performed throughout the R&D process to help demonstrate a powder's flow characteristics. A thorough process development, including conducting BU and CU studies and determining turret and feeder speed, also helps optimise production and reduce time involved in troubleshooting.

Minor powder flow issues during R&D can turn into major headaches once scale-up to industrial production begins. Conducting studies throughout R&D and scale-up can help identify and isolate where in the process a formulation issue began. Powder flow also can vary from lot to lot, which needs to be understood during R&D. Most problems that manifest on the tablet press start with the powder and its flow properties, so it's important to understand how a powder will perform under every circumstance.

ABOUT THE COMPANY

Natoli Engineering Company is a world-leading company in tablet-press tooling manufacturing. Founded on the principle of manufacturing and delivering the highest quality products at a fair price with exceptional customer service, Natoli continues to build on 40 years of innovation and industry leadership.

ABOUT THE AUTHOR

Jonathan Gaik received his BS in Chemistry from the Missouri University of Science and Technology (Rolla, MO, US). He has worked in solid oral dosage formulation and process development in the pharmaceutical and food industries. Mr Gaik has various patent applications for his work combating the opioid crisis via abuse-deterrent dosage forms. His current interest is driving the development of continuous manufacturing and identifying first principles sources of solid oral dosage formulation-related issues during processing. Mr Gaik is currently director of Natoli Scientific and co-director of the Natoli Institute for Industrial Pharmacy Research and Development at the Arnold and Marie Schwartz School of Pharmacy at Long Island University (NY, US).