

Go with the flow

A perfect active pharmaceutical ingredient is one that performs well from R&D through tablet production. However, in real-world situations challenges are inevitable. Here, Jonathan Gaik, director, Natoli Scientific, looks at the critical issue of powder flow and how solving issues before production can reduce product performance issues later down the line.

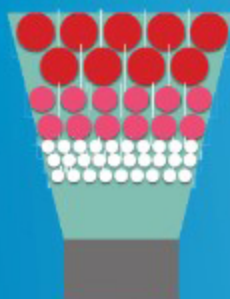


FIGURE 1. PARTICLE SIZE AND DENSITY VARIATION WITHIN A HOPPER

The ideal active pharmaceutical ingredient (API) is 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 continues to be critical is powder flow. Most challenges in the tableting process initiate with or can be traced back to flow.

Product flow challenges become more apparent when scaling up to full production. A seemingly minor product fault during R&D can become unmanageable during production. 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.

STORAGE CONDITIONS

Humidity 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 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. These issues are most likely due to improper storage, a poorly selected binder

that is too cohesive with the API, lack of glidant, improper order of addition, or an incorrect blending procedure.

The best way to establish flowability is to compare flow on a Flodex powder flow tester with the tablet configuration to determine whether the powder's intrinsic flow is close or equivalent to the cross-section of the die. For example, a Flodex may show a neat API powder has flowability of 26 mm, with a round tablet design of 12 mm in diameter. The formulator needs to look at 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 preblend step to maximise the interaction between the glidant and the poorly flowing materials. A preblend step usually lasts between two and eight minutes, and the length of this step can be determined using a Flodex. Blend uniformity (BU) studies ensure APIs are adequately blended with excipients and can

give formulators clear evidence of whether a formulation is within specification before moving to the next step.

HOPPER DESIGN AND POWDER SEGREGATION

After blending, the powder will be discharged to the hopper, where the formulator must ensure adequate flow properties to successfully enter the gravity or force feeder. Difficulties when discharging a powder blend 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 vibration from the tablet press causes larger

particles to separate from the smaller particles. Smaller particles filter to the bottom while the larger particles rise to the top (Figure 1). 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 high ejection forces. Conducting content uniformity (CU) studies, which should follow the guidelines set forth by the US FDA under 21 CFR 211.110, can help determine whether the batch is consistent and within specification.

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 sits under the opening in the feed frame for a small amount of time, usually milliseconds. Therefore, the flow rate must be calculated and tested to ensure the powder can keep pace with the feeder and turret speed and adequately fill 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.

Turret and feeder speed must also be matched to the flow rate of the powder to prevent overblending, which can result in segregation or excessive lubrication and thus can 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 within the acceptable content uniformity range. CU2 shows an example of sifting segregation, while CU3 shows irregular, non-uniform tablet content due to overblending.

CU samples can help identify specific problems based on the results; however, unless they are paired with BU studies they will not be able to isolate where the issue is occurring. Changes in hardness can be identified with the same CU studies.

Finally, poor powder flow can result in tablet defects such as sticking and picking, which may be caused by entrapped air within the 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 result 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, to improve powder flow.

ENSURING GOOD POWDER FLOW

A poorly flowing powder can affect tablet quality at every step in the process.

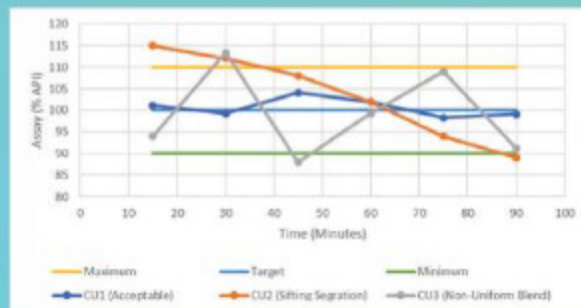


FIGURE 2. TABLET CONTENT UNIFORMITY ASSAY STUDIES

Key factors to consider when encountering a powder that doesn't flow well are formulation design, storage conditions, tablet design and mechanical design of processing equipment. Powder rheology studies, such as shear strength and wall friction, which can be conducted on a Freeman FT4, and flowability 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, 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 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 can also 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.

Working with a trusted partner, such as Natoli Scientific, can help identify and address potential formulation concerns before moving into production to reduce product performance issues.

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