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Review article

Mini review: Mechanisms to the loss of tabletability by dry granulation

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ABSTRACT

In this mini-review, we have critically examined literature aimed at understanding the mechanisms to the frequently observed phenomenon of loss of tabletability of a powder after dry granulation by slugging or roll compaction. Impact of each mechanism on tabletability could be explained by considering their influence on either bonding area (BA) or bonding strength (BS). For plastically deforming materials, key mechanisms that influence tabletability of dry granulated powders include lubrication, granule size enlargement, and granule hardening. The use of more lubricant leads to lower BS and reduced tabletability. Compared to external lubrication, internal lubrication tends to exhibit more detrimental effects on tabletability. If extensive fragmentation can be avoided, granules with a higher porosity (or lower solid fraction) are more deformable under compaction pressure to favor larger BA and stronger tablet. For brittle materials, granule hardening can still be important despite they are relatively less prone to the lubrication problem. Not surprisingly, there is not a single mechanism that can explain all observations. The dominating mechanism in each specific case depends on material properties and process parameters. We have summarized a total of eight important aspects that should be addressed when developing a dry granulation (DG) process. We have also presented four golden rules to be considered when dealing with the dry granulation process.

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1. The problem

In pharmaceutical tablet manufacturing, poor powder flowability leads to processing difficulties, such as poor mixing, inconsistent die filling, and low efficiency in powder blending and transportation. An effective and commonly employed approach for overcoming problems related to poor flowability is size enlargement through granulation. Granulation achieved without using any liquid has several advantages, including simpler process than wet granulation and no need for drying. The recently introduced manufacturing classification system [1] has placed dry granulation (DG) between direct compression (DC) and wet granulation (WG) in terms of simplicity of manufacturing. Historically, dry granulation was done by slugging followed by milling. Modern dry granulation involves the use of roll compaction (RC) to compress a loose powder into ribbons, which yields granules on subsequent milling [2].

The ability of a powder to be transformed into tablets with certain strengths under prescribed pressures has been termed either compactibility or tabletability (tablet tensile strength vs. pressure). Both terms have been extensively used in the open literature to describe the dependence of tablet tensile strength on compaction

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pressure [3,4]. Either term is acceptable as long as it is defined in each publication. The term "tabletability" is used in this review. A long-recognized common problem in implementing a dry granulation process is the phenomenon of loss of tabletability, or reworkability, of granules [5]. Here, we will critically review current literature to arrive at a clear understanding of the mechanisms involved in this phenomenon. Such understanding is essential for designing a robust DG process and for identifying an effective solution to the loss of tabletability problem, if encountered [6]. Since the problem at hand pertains to tablet mechanical strength, it is useful to recognize that tablet tensile strength is determined by the interplay between bonding area (BA) and bonding strength (BS) [7,8]. Larger BA among granules or higher BS favors stronger tablets. Any factors that influence either BA or BS will impact powder tabletability accordingly.

2. Quest for the mechanisms

Several mechanisms have been proposed to explain the loss of tabletability phenomenon in DG. However, the clear assignment of the importance of the different mechanisms is difficult due to some complications:

(1) The moisture content of a material can influence its deformation behavior and the tensile strength of the resulting tablets. Therefore, dominating mechanism to loss of tabletability can be influenced by moisture content. Unfortunately, relative humidity is not always controlled or specified in published papers, which makes a direct comparison difficult because even the "same" material may behave quite differently in different studies.

(2) The lubricant can significantly affect the tensile strength of tablets for some materials. Amount of lubricant and the way of addition are of major importance [9]. Furthermore, different crystal forms of the same lubricant, e.g., magnesium stearate, or its specific surface area can exhibit very different lubrication efficiency.

(3) The applied force or pressure during roll compaction is an important factor that influences the degree in loss of tabletability. For the same material, the degree of loss in tabletability may be marginal if the applied force or pressure is low, but can be substantially large at a high applied force or pressure. Granules obtained under a lower roll pressure are more porous, which can deform or fracture more easily during subsequent tableting. Hence, they exhibit higher tabletability. Unfortunately, the different suppliers of roll compactors offer various parameters for roll pressure control. Some provide the specific compaction force in kN/cm, which is the applied compaction force per cm of roll width. Others provide a hydraulic pressure, which is not equal to the pressure applied to the material. Since conversion factors are usually not easily available or routinely given in a paper, it is difficult to directly compare roll pressure in studies employing different roll compactors. In fact, the actual applied pressure is often not known. Fortunately, porosity of the ribbons or granules can be measured. Therefore, it is a good practice to report porosity of granules or ribbons in DG research when possible. This way, data interpretation is more reliable and comparison of results from different studies is much easier, even when different equipment is used.

(4) A given chemically pure material may exhibit very different physical properties, which are important for the effect of loss in tabletability. For example, many APIs and excipients are available in different physical forms, including polymorphs, solvates, and amorphous form. Even when the solid phase is the same, batch-to-batch differences in particle size, morphology (crystals vs. agglomerated), shape, surface roughness, etc., can also exist. Consequently, behaviors in roll compaction and tabletability can be very different for the chemically identical materials.

If not carefully taken into account, these factors can result in biased conclusions from a DG study. For the clear distinction of the different mechanisms, studies may have to deviate from real life situations and be performed in an artificial way. In addition, the used materials should be described in detail. The relative humidity should be kept constant and DG should be performed at different specific compaction forces over an appropriate range. The granules should be classified into different sieve fractions and each sieve fraction should be tableted at different pressures. The mode of lubrication should also be considered since external lubrication, where tool surfaces are covered with lubricant, and internal lubrication, where lubricant is mixed with the powder, can lead to very different granule properties. If studying loss in tabletability is the aim of a study, a powder blend before roll compaction must be included as a reference. Since usually only some of the above-mentioned points are taken into account in a given paper, seemingly conflicting conclusions had been made in different studies. A main goal of this paper was to critically assess some relevant papers concerning the mechanism to the phenomenon of loss of tabletability after DG, with special attention on their experimental designs critical for reaching respective conclusions.

Work hardening is one of the earliest hypotheses proposed to explain the phenomenon [5]. Malkowska and Khan described work hardening as the "production of robust granules, which have increased resistance to deformation". This phenomenon is more significant, if the initial compaction when making slugs or ribbons was performed at a higher pressure. Pregelatinized starch, microcrystalline cellulose (MCC), and dicalcium phosphate (DCP) were included. Sieve fractions (100–160 μm for starch and 32–160 μm for MCC and DCP) were used. No magnesium stearate was added to MCC and starch but 0.5% magnesium stearate was added to DCP. Slugging was performed at two different pressures (23 and 70 MPa for starch and 9 and 28 MPa for MCC and DCP). After milling, the same sieve fractions as that for initial compression were used for re-compression. For DCP granules, again 0.5% magnesium stearate was added. Re-compression was performed up to 120 MPa for starch and 50 MPa for MCC and DCP. The reworking potential was expressed as the ratio of the areas under the tabletability curve of the recompression and the first compression in %. Under such conditions, the reworking potential was the lowest for starch and the highest for MCC. For all materials, a higher slugging pressure reduced the reworking potential. It is interesting to note that the reworking potential was lower for the brittle DCP than for the plastic MCC, which was about 85% at the higher slugging pressure of 28 MPa. As we will discuss later, this relatively low slugging pressure only leads to a small loss in tabletability even for plastically deforming materials. In addition, magnesium stearate was added to DCP but not to other materials. It is also unusual to take the same sieve fraction from the DG material as from the starting material, because DG is performed for particle size enlargement. This practice effectively minimized the chance of observing potential effects on tabletability due to size difference. In fact, when taking the powders as such, instead of a sieve fraction, and with 0.5% of magnesium stearate added, the reworking potential for MCC and DCP was both markedly lower. This landmark study in the quest for a clear understanding of the phenomenon has taken some of the critical points into account, although the choice of the low slugging pressure and the use of