Development of New Laboratory Tools for Assessment of Granulation Behavior During Bulk Active Pharmaceutical Ingredient Drying

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ABSTRACT: Approximately 30% of active pharmaceutical ingredients (APIs) experience agglomeration, granulation, and breakage during agitated drying. Currently, there is no small-scale bench tool to help assess and observe granulation behavior of APIs in the laboratory and subsequently lead to the development of a robust drying method. As a result, more conservative drying methods are usually used at scale and much longer drying times are needed. In this work, we build on work reported in the literature and demonstrate that a mixer torque rheometer (MTR) can be a useful small-scale tool to flag potentially problematic granulation behavior of APIs under different conditions. The results from the MTR were confirmed using a second new tool involving the use of an acoustic mixer to verify and observe the granulation behavior on a small scale. We also show consistency between the data collected at the laboratory and the pilot plant scales.
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INTRODUCTION

To deliver drug substances for further formulation into drug products, active pharmaceutical ingredients (APIs) are commonly purified by crystallization and solvents are removed by filtration and drying unit operations. During drying, mechanical agitation of the wet cake is often employed to enhance heat and mass transport and speed up the drying process. For some compounds, the use of continuous agitation can lead to the formation of agglomerates or granules in the final delivered dry cake or breakage of the primary particles.[1–4] This can lead to particle size distributions (PSDs) that do not meet the required specifications needed for further processing and formulation into the final drug product. If the desired physical attributes cannot be achieved through milling or other dry processing steps, a wet reprocessing of the material will be required if possible or, in the worst case, the material may need to be discarded. Even if the material can be reprocessed, the added processing steps, wet or dry, are not desirable and can lead to increased costs and production delays. In the absence of a bench-scale tool to study and predict the granulation behavior of APIs during drying in pilot or commercial scales, engineers will usually choose a more conservative drying method with minimal amount of agitation to avoid additional processing steps. Although granulation may be avoided in this manner, this is far from ideal and much longer drying times are typically needed because of less effective heat and mass transfer caused by nonoptimal agitation protocols.[3]

For development on the drug product side, a mixer torque rheometer (MTR) has been explored as a more systematic way to monitor wet granulation instead of less sophisticated and subjective methods such as hand squeezing.[5] The geometry of the mixer and the mixing kinetics have been shown to be important in the characterization of rheological behavior.[6–8] Most recently, a group from Pfizer has started employing a MTR for drug substance process development to help study agglomeration of APIs during drying.[1,2] In the work described in this article, the performance of the MTR is assessed systematically as a predictive tool of API granulation behavior and its direct linkage to observations at the pilot scale. An analysis of the measurement system itself was carried out first to determine the effect of key instrument operating parameters such as bowl type (full vs. half), solids mass loading, mixing time, and impeller mixing speed. After demonstrating the robustness of the measurement system, material-based factors such as compound, starting particle size, and solvent system were also studied. The relationship between the critical solvent content (or "risky zone") obtained from the MTR and granule formation during agitation was confirmed using a second new tool involving an acoustic mixer to verify the behavior on small scale. Lastly, the consistency between the MTR assessment and pilot-scale performance was also shown.

EXPERIMENTAL

Mixer Torque Rheometer

The built-in multiple addition method on a Caleva Mixer Torque Rheometer 3® system (Caleva Process Solutions Ltd., Sturminster Newton, UK) was used for all MTR experiments unless otherwise stated. This method provides a rapid way to gain information on the critical solvent content that may promote granule formation, but has limited capability to describe binding kinetics and strength of any granules that may form

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(another tool, described later, is used for this). Typically, in the multiple addition method, torque of the empty bowl was recorded for 20 s and used as a baseline to normalize all subsequent measurements with solids present. Dry mass was then loaded, mixed for 20 s and the torque response was recorded for an additional 20 s. The effect of cake solvent content on the flowability of the solids was determined by adding solvent and performing subsequent torque measurements. After each addition of solvent, the wet mass was mixed for 60 s and torque recorded for 20 s. The averaged torque recorded after each solvent addition was then plotted against the solvent content of the wet mass. As the API mass transitions from a dry cake to wet slurry on the MTR, it goes through different states of liquid saturation, including pendular, funicular, capillary, and droplet.[5] A maximum in the torque response is expected within the capillary state because of the liquid bridging between particles. The solvent content at which this is observed in the MTR is considered the critical solvent content and the breadth of the maximum peak defines the "risky zone" for granulation to occur during agitated drying.

Design of Experiment

A four-factor half-factorial experimental design was executed using Compound A in a full bowl setup on the MTR. In these experiments, a jet milled version of Compound A was used to enhance the response from the MTR because smaller particles of this compound are known to have higher tendency to form agglomerates and granulate. The temperature was controlled at 20°C using the built-in jacket of the mixing bowl. The factors in this design of experiment (DOE) included (a) mixing speed, (b) mixing time, (c) fill/load, and (d) volume percent methanol (MeOH) in the MeOH/water solvent system. All solvents used in this DOE were first saturated with Compound A to more closely mimic the conditions present during drying. The ranges of the instrument parameter selected were limited by the capabilities of the MTR. Material parameter ranges were limited by the compound physical properties (particle size, density, and solubility).

Acoustic Mixer ("Lab Granulator")

Granulation behavior was observed using an acoustic mixer lab granulator. The granulation assessment tool consisted of a cylindrical glass container with Teflon end caps mounted on top of a LabRAM® acoustic mixer (Resodyn™ Acoustic Mixers, Inc., Butte, MT) (Fig. 1). A temperature probe and a filtered vacuum port were installed onto the top-end cap. Temperature was controlled using external electrical heat tracing, vacuum level was set using a gauge and bleed system, and mixing was achieved by setting the LabRAM® vibration to the target mixing intensity. The design provides conditions conducive to granule formation by allowing for a tumbling motion while subjecting the solids to higher forces than can be applied using scaled down versions of typical drying equipment.

For all experiments, the typical force was set at 40 times the acceleration of gravity (G). This parameter was set somewhat arbitrarily but resulted in the desired solids motion within the container being used while at the same time supplying a sufficient compressive force to induce granulation. Wet cakes were prepared by filtering a slurry of API until no free liquid was observed flowing. In some cases, the solvent content of the wet cake was adjusted by either adding more solvent to the filter cake or by partially drying in a vacuum oven without agitation. In other cases, the starting solvent content was varied to see the impact on granulation. For these runs, approximately 30 g samples of wet cake with different loss on drying (LOD) were loaded, and each run was conducted over 2 h. Additional experiments were conducted using the same compound with different starting particle size to assess the impact of this parameter. The impact of solvent system on granulation behavior was also assessed. In these experiments, approximately 50 g

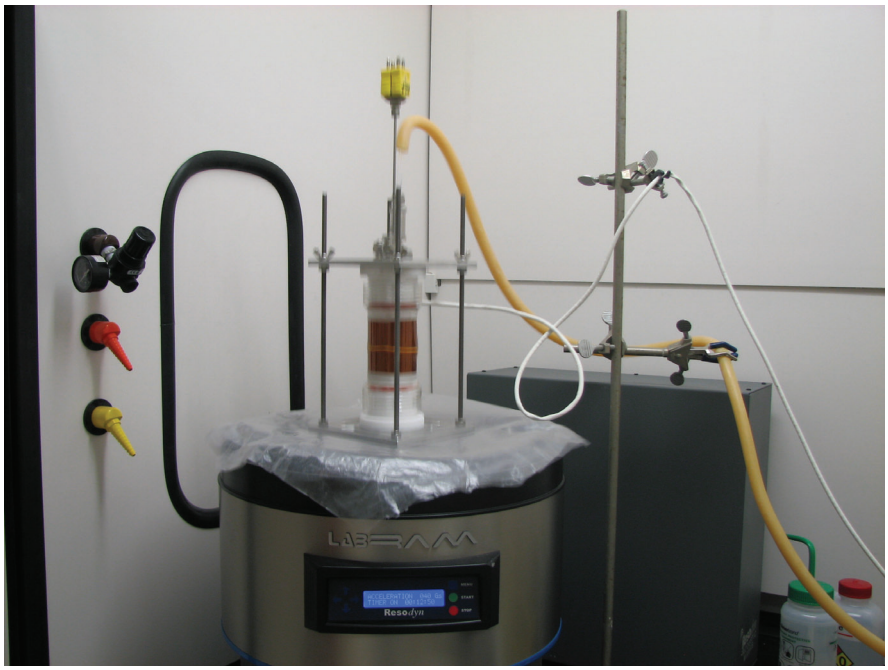

Figure 1. Photo showing setup of the acoustic mixer with column jacketed with electrical heat tracing. The vacuum line and temperature probe can be seen protruding from the top-end cap.