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The effects of improper mixing and preferential wetting of active and excipient ingredients on content uniformity in high shear wet granulation

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ABSTRACT

This work focuses on the content non-homogeneity in granules across size classes in a high shear wet granulation process as a result of powder segregation during dry mixing coupled with preferential wettability of one of the ingredients with the binder fluid.

A two component API-excipient system comprised of acetaminophen (APAP) and microcrystalline cellulose PH-101 (MCC) is investigated in a high shear granulation environment for content uniformity of the granules with respect to APAP. It was found that the fine granules were super potent while the coarse granules were starved of the APAP. This was attributed to a dual cause of powder segregation during dry mixing and superior wettability of the MCC compared to APAP. Post the dry mixing stage, the top layer of the powder bed is found to be sub-potent due to percolation of the smaller APAP particles to the bottom of the bed as they find spaces between the larger MCC particles. Thus, a drop of the binder fluid which falls on the bed is likely to be surrounded by MCC particles, which give them a higher chance of being incorporated in the nucleus. Moreover, MCC being the superior wetting of the two ingredients, also preferentially attaches itself to the growing granules. The granules are thus starved of the APAP leading to disparity in content across size classes.

Lastly, the effect of content non-uniformity was categorically quantified on the rate of active release. It was observed that content non-uniformity results in a lack of predictability and consequently control, on the rate of release of the active ingredient from the granules. This work highlights the need for qualitative understanding and quantitative analysis of factors that contribute to the occurrence of granule content non-uniformity, if one is to enable inherently robust pharmaceutical product design.

1. Introduction and motivation

High shear wet granulation is a particle size enlargement process in which a powder assembly is vigorously mixed with a liquid binder to induce particle growth [1,2]. Typically, size enlargement is accompanied by increased bulk density and superior flow, making the powders amenable to today's high speed tableting processes [3]. Granulation is thus an integral step in the manufacture of a large volume of pharmaceutical solid oral dosage forms (tablets and capsules). In addition to the aforementioned extrinsic changes, granulation also causes change in the microstructure of the particles, namely, porosity and morphology, thus enabling a degree of control over dissolution characteristics of the final product [4,5].

However, one of the most important necessities for granulation is to ensure homogeneity of the formulation ingredients, especially in the case of low dosage products. Wet massing of the ingredients should result in granules which are homogeneous in content. They are expected to contain the active pharmaceutical ingredient (API) and the excipient in the same proportion as the original bulk mixture. Thus, despite the ability of some formulations to be directly compacted (despite good compaction characteristics and flow properties), they are granulated to improve confidence in content uniformity.

Ironically, that may not always be the case. It has often been observed that granules exhibit a non-uniform distribution of the API across size classes [6–10]. The active ingredient may show a preferential tendency to accumulate in the coarse or the fine granules.

Several mechanisms have been proposed to explain the cause of an uneven distribution of ingredients during high shear wet granulation [6–11]. The solubility of the active ingredient and particle size has

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been identified as key properties that play an active role in uniform distribution of the drug across granule size fractions.

Egermann and Reiss [6] observed that the ingredient with the smaller primary particles was accumulated in the coarse granules. The results were corroborated by Vromans et al. [7] and van den Dries and Vromans [8], who both showed that the finer primary particles produced stronger granules and had sufficient strength to resist shear forces. This led to the accumulation of the finer ingredient in the coarse granule fraction. Thus, if the primary particle size of the active ingredient was smaller than the filler material, the coarse granules were found to be super-potent and vice versa.

The solubility of the ingredients in the binder fluid was also found to play a part in their distribution across size fractions. Ojile et al. [9] observed that a soluble drug dissolves in the binder liquid and consequently the distribution of the drug depends on the distribution of the binder fluid within the granulated mass. Over-wetted regions were thus found to be super-potent, while under-wetted regions were starved of the drug. Another intriguing effect of drug solubility is the non-homogeneity it can cause due to migration of the binder, and consequently the drug, during drying of the wet mass. It was found that the drug-rich solute is leached to the surface of the granules during drying [10,11]. The fluid evaporates, leaving deposits of the drug on the crust. These deposits are loosely attached and thus fall off during subsequent powder handling operations, leading to a high concentration of the drug in the fines.

Inhomogeneity in high shear granulation is therefore a complex phenomenon, the cause of which depends on at least two properties of the ingredients. However, all of the above work assumes that the powder bed being wetted is well-mixed. The state of the mixture being wetted is completely random and thus, the probability of a binder-drop being surrounded by API/excipient particles is proportional to the original weight fractions in the bulk mixture. The subsequent formation of a nucleus will be dependent on the properties of the powder ingredients and the binder fluid, but both ingredients will have a proportional chance to be wetted and get incorporated in the nucleus.

It is thus of interest to investigate a system in which the properties of the powder ingredients being granulated are very different from each other and consequently pose a mixing (dry mixing) challenge. It is well known that a difference in particle size, density or particle shape of granular ingredients can cause granular materials to de-mix [12]. Granular mixing in bladed mixers (geometry of interest) has been well studied [13,14]. Researchers have reported various segregation patterns depending on shear levels within the mixer and disparities in the particle sizes of the ingredients being mixed. Thus, if the powder mixture being wetted is poorly mixed, then a drop of the binder fluid that falls on the powder bed can be disproportionately surrounded by one of the ingredients, leading to disproportional incorporation of the ingredient within the nucleus and consequently, perhaps, the granules.

Coupled with the above phenomenon, a significant difference in the wettability of the components amplifies the challenge of achieving homogeneous granules. It is well known that the presence of hydrophobic components in the formulation can lead to poor wetting of the powder bed by the binder fluid, resulting in a non-uniform distribution of the formulation ingredients. Fundamental work on the wetting behavior of the powder mixtures was carried out by Lerk et al. [15] and Aulton and coworkers [16]. The work was extended by Nguyen et al. [17], who systematically varied the proportion of the hydrophobic component to quantify its effect on granule uniformity. It was found that achieving content uniformity in granules becomes more difficult with increasing proportions of the hydrophobic component due to granulation competition that arises between the hydrophobic and hydrophilic components. Cavinato et al. [18] reported a similar finding and stated that for those drug compounds that exhibited poor wettability, the liquid distribution within the powder bed was poorer, leading to selective agglomeration and non-uniform drug distribution.

The aim of this work is to investigate the cause of drug non-uniformity across granule size classes in a high shear wet granulation process. More specifically, the study focuses on non-uniformity that can be caused by imperfect mixing of granular ingredients in the dry mixing stage. Coupled with imperfect mixing, the study quantifies the nature of poor drug distribution that arises due to a significant difference in the wettability of the powder ingredients. Two exclusive causes of poor drug distribution have been combined in a single study to provide a more complete understanding of the phenomenon. The active load, impeller speed and wet massing time have been employed as design variables to assist in the comprehension of the abovementioned causative agents.

Lastly, the effect of content non-uniformity and its impact on release kinetics of the active ingredient is examined. Several studies have considered the effect of granulation process parameters on the release kinetics of the active ingredient from the granules [19–21]. However, investigations that categorically quantify the effect of content non-uniformity on release profiles are lacking. This study attempts to make an early in-road in that direction by elucidating the impact of process parameters on content non-uniformity and subsequent release kinetics.

2. Materials and methods

2.1. Materials used

Micronized acetaminophen (APAP, Mallinckrodt Inc., Raleigh, NC) was used as the API and microcrystalline cellulose (Avicel PH-101, FMC BioPolymer, Philadelphia, PA) was the excipient. Water was used as a binder. Ethyl alcohol (>99.8%) for UV/VIS spectroscopy was purchased from Lachner. Water for the UV/VIS spectroscopy was purified by a demineralized water generator (Aqual 25) to a conductivity of ~1 $\mu S \cdot cm^{-1}$. All experiments were performed at room temperature.

2.2. Formulation of material characterization

2.2.1. Primary particle size

The primary particle size of the ingredients was measured using a laser light diffraction technique (Beckam Coulter LS 13 320). Each measurement was repeated in triplicate and the average value is reported in Table 2.

2.2.2. Contact angle

The contact angles for APAP and MCC with water were determined using the Washburn capillary rise method, where the rate of liquid rise through a powder bed due to capillary action is measured. The Washburn equation in terms of mass of liquid that penetrates a column of powder is given by the following equation:

$$t = \frac{\eta}{C\rho^2\gamma\cos\theta} m^2$$

where m is the mass of the liquid that penetrates the column with time t, η is the liquid viscosity, γ is the liquid surface tension, θ is the contact angle and C is the capillary constant.

The apparatus consisted of a glass cylinder fitted with a ceramic membrane at the bottom, and is shown in Fig. 1. The column was first cleaned by washing it with water followed by hexane and lastly by rinsing it with acetone. It was then dried at 100 °C for 15 min in a hot air convection oven and packed with the material whose capillary rise was being measured. The column was then subjected to 2000 taps at a frequency of 250 taps per minute on a Quantachrome Autotap (Quantachrome Instruments, Boynton Beach, Florida; Model Number: 2106-60-01). The tapping ensures a uniform packing architecture for each measurement for a given material. The column was attached to a