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Research paper

Analysis of the origins of content non-uniformity in high-shear wet granulation

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ABSTRACT

In this study, the origins of granule content non-uniformity in the high-shear wet granulation of a model two-component pharmaceutical blend were investigated. Using acetaminophen as the active pharmaceutical ingredient (API) and microcrystalline cellulose as the excipient, the distribution of the API across the granule size classes was measured for a range of conditions that differed in the duration of the initial dry mixing stage, the overall composition of the blend and the wet massing time. The coarse granule fractions were found to be systematically sub-potent, while the fines were enriched in the API. The extent of content non-uniformity was found to be dependent on two factors – powder segregation during dry mixing and redistribution of the API between the granule size fractions during the wet massing phase. The latter was demonstrated in an experiment where the excipient was pre-granulated, the API was added later and wet massed. The content non-uniformity in this case was comparable to that obtained when both components were present in the granulator from the beginning. With increasing wet massing time, the extent of content non-uniformity decreased, indicating that longer wet massing times might be a solution for systems with a natural tendency for component segregation.

1. Introduction

Content uniformity is a key quality attribute of pharmaceutical products. The presence of sub- or super-potent product in a batch is not acceptable, as it might not only impair the efficacy of the prescribed treatment regime, but for some medicines it might be outright dangerous to the patient. In the case of solid dosage forms such as capsules or tablets, the high-shear wet granulation process is often employed in order to convert the primary particles of the active pharmaceutical ingredient (API) and excipients into larger granules, which possess the required mechanical and flow properties that are necessary for tabletting or capsule filling (Shi et al., 2011a, 2011b). The variability of API content in the final product (capsules or tablets) should not deviate from the nominal dose. If the API content across individual granule size classes is highly non-uniform, there is a danger that this non-uniformity will also be reflected in the final product due to size segregation that can occur when feeding the granules into the tablet press or the capsule filling machine (Mateo-Ortiz et al., 2014; Guo et al., 2011; Johansen et al., 1989). However, even if such size segregation does not occur, the non-uniformity of API content across the granule size classes is still undesirable, as it may influence the release profile of the API during dissolution (Oka et al., 2015; Kašpar et al., 2013), and consequently the pharmacokinetic profile of the drug in the patient.

The high-shear wet granulation process consists of several steps: dry blending, binder addition and wet massing, which are followed by drying and milling (Emady et al., 2016; Parikh, 2017). In principle, the origins of content non-uniformity can lie in any of these steps. During the dry blending stage, the raw materials (API and excipients) that are fed into the granulator bowl are mixed in the dry state to homogenize the mixture before the liquid binder is added. Segregation of the components can occur during this stage, depending on the particle size and material density of the formulation ingredients, and the mixing conditions (rpm and duration) (Oka et al., 2015, 2016; Radl et al., 2010; Conway et al., 2005; Watano et al., 2000). During binder addition, the difference

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in the surface wettability of individual formulation components (Nguyen et al., 2010) can potentially favour or suppress their interaction with the binder droplets and incorporation into the granule nuclei, and eventually lead to content non-uniformity. During wet massing, elementary rate processes such as coalescence, breakage and consolidation (Iveson et al., 2001; Litster and Ennis, 2013) can influence the re-distribution of individual components across the granule size classes (van den Dries and Vromans, 2002, 2003; Vromans et al., 1999). Finally, the drying stage can lead to a non-uniform API distribution within individual granules due to capillary transport in the granule structure (Kiekens et al., 2000, 1999; Kapsidou et al., 2001; Poutiainen et al., 2012; Ridgway and Rubinstein, 1971; Schrank et al., 2014). If this is coupled with granule attrition during subsequent granule handling operations such as sieving or transport, again there is potential for content non-uniformity.

In order to design a robust manufacturing process and minimize the potential for content non-uniformity in the final product, it is important to understand if and how the individual steps of a high-shear wet granulation process contribute to the final distribution of the API across the granule size classes. The purpose of the present work was therefore to design and perform a series of experiments that would allow us to confirm or reject hypotheses about the origins of content non-uniformity. Specifically, the influence of the dry mixing stage, the binder wetting stage and the wet massing stage on the API distribution across the granule size classes was systematically investigated for a range of compositions of a model pharmaceutical formulation, consisting of acetaminophen as the active pharmaceutical ingredient (API) and microcrystalline cellulose as the excipient.

Overall, this work was conceived as a series of experiments aimed at confirming or rejecting possible hypotheses about the origins of content non-uniformity. The following hypotheses were considered:

H1. The reason for content non-uniformity is preferential wetting of one formulation component by the binder during the wetting and nucleation stage due to different surface properties (wettability) of the particles.

H2. The reason for content non-uniformity is particle segregation during the dry mixing stage, which would result in the enrichment of the powder bed surface by one of the components and therefore its preferential contact with the binder.

H3. The reason for content non-uniformity is different kinetics of elementary rate processes (agglomeration, layering, attrition, breakage), which are composition-dependent in such a way that they lead to systematic enrichment of certain size classes by one of the formulation components.

The first hypothesis was tested by drop penetration experiments, whereby the composition of a nucleus formed from a single droplet deposited onto a well-mixed powder bed was analysed and compared with the nominal bed composition. The second hypothesis was tested by varying the duration of the dry mixing phase of a granulation experiment and evaluating the relationship between the dry mixing time and content non-uniformity in the final granules. The third hypothesis was tested by varying the duration of the wet massing phase, and starting the wet massing phase from both well-mixed and maximally segregated initial conditions (these were created by pre-granulating the excipient and only then adding the API, thus simulating a hypothetical scenario in which nucleation would be 100% selective towards the excipient).

2. Materials and methods

2.1. Materials

A two-component model pharmaceutical formulation was used for the purpose of this study. Micronized acetaminophen (Mallinckrodt, St. Louis, MO) was chosen as the active ingredient and microcrystalline cellulose (Avicel PH-101 FMC Biopolymer, Philadelphia, PA) was chosen as the excipient. The particle size distribution parameters and bulk density of the ingredients are reported in Table 1. 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. Bulk density of the ingredients was measured by calculating the volume occupied by a known mass of material as it was poured in a graduated cylinder using a funnel. Each measurement was repeated in triplicate and the average value has been reported in Table 1. Deionized water was used as a liquid binder in all experiments. Ethanol for UV/vis spectroscopy (>99.8% purity) was used as solvent for API content determination.

2.2. Nucleation experiments

Mixtures of microcrystalline cellulose and different amounts of acetaminophen (3, 7, 20 and 30 wt%) were first homogenized in a Turbula mixer (50 rpm, 10 min). A powder bed was prepared by sieving each mixture through a 1.5 mm mesh size sieve into a Petri dish (8 cm diameter, 1 cm depth). Redundant material over the level of the Petri dish edges was scraped off in order to create a flat surface. Deionized water was added to the powder bed as a single droplet by a syringe through a 22 gauge needle. The tip of the needle was 5 mm above the powder bed surface in order to achieve a low Weber number impact (no crater formation or splashing). The formed nucleus was gently scooped out from the powder bed and placed into liquid nitrogen in order to obtain a solid, and sufficiently strong agglomerate for further manipulation. Each nucleus was dried, weighed and dissolved in ethanol to determine its composition by UV–vis spectrophotometry (acetaminophen (APAP) is soluble in ethanol while microcrystalline cellulose (MCC) is not). Five repetitions for each APAP:MCC mixture were carried out.

2.3. Granulation experiments

Granules were prepared by a laboratory high shear granulator KG5 (KEY International Inc., NJ) with a 3.9 L, 20.5 cm diameter stainless steel bowl equipped with a blade chopper for the disintegration of bigger agglomerates. The chopper speed was maintained at 6500 rpm and the main impeller speed was 225 rpm. The batch size for all experiments was 250 g with three different API loads (3, 7 and 20% wt.) and a constant binder/solids ratio of 0.8 (200 mL of deionized water). Before actual granulation, pre-blending of the dry mixture was conducted for different times (0, 0.5, 2 and 5 min). The complete experimental plan is summarised in Table 2. After each pre-blending step, small samples (about 100 mg) were collected from the powder bed surface at 8 different positions in the granulator for the analysis of API content. The sampling points were located at 3, 6, 9 and 12 o'clock positions,

Table 1
Particle size distribution parameters and bulk density of the pure ingredients.

PSD parameter (μm)	d10	d50	d90	Bulk Density (g/cc)
μ- Acetaminophen	2.9	10.9	31.6	0.2
Microcrystalline Cellulose PH101	16.5	57.6	132.4	0.33