Improving blend content uniformity via dry particle coating of micronized drug powders

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Abstract

Content uniformity of low dose blends with fine active pharmaceutical ingredients (API) is adversely impacted due to API agglomeration caused by high powder cohesion. Dry coating using high-intensity vibratory mixing is employed to reduce API cohesion and granular Bond number as well as agglomeration as predicted by contact models, hence improve blend content uniformity (CU). Micronized acetaminophen (mAPAP) ($\sim 10\text{ }\mu\text{m}$), a model API, was dry coated with nano-silica R972P (20nm), and mixed with Avicel 102. The amount of silica was varied from 0 to 2.74 wt %, corresponding to theoretical surface area coverage (SAC) from 0 to 100 % respectively. Bulk density, unconfined yield strength, and dispersive surface energy results indicated dry coating with 0.27 to 1.0 wt % silica was adequate for API property enhancement; further corroborated by improved CU for 5 wt % API blends. Excellent CU was achieved for 3, 5 and 10 wt% API loaded blends, where 30 minutes of mixing was found to be acceptable for all three. The CU with dry coated mAPAP was significantly lower and within the acceptable range as compared to control blends without silica, as well as those with silica added during blending. Sieving of mAPAP illustrated the reduction in mAPAP agglomeration, necessary for improved CU after dry coating, corroborating model based predictions. Compared to theoretical predictions, actual CU was higher unless API agglomerate size distribution obtained via sieving was taken into account. Overall, cohesion reduction by dry coating is shown as a promising approach for improving content uniformity of cohesive API blends.

Key words: content uniformity, low dose blends, cohesive API powder, dry coating, granular Bond number

1. Introduction

The uniformity of active pharmaceutical ingredients (API) in pharmaceutical dosage forms, such as tablets, capsules and packaged suspensions, is one of the most important drug product quality attributes (Kupiec et al., 2008). For low dose tablets, although blend uniformity and tablet content uniformity may not be fully correlated, the comparison between the two attributes may offer further insight into the possible manufacturing problems (Bergum et al., 2014b; Garcia et al., 2014). Therefore, understanding of the factors affecting blend uniformity is very important. To address the issues raised after the withdrawal of the FDA draft guidance (FDA, 2003) on this subject, the Blend and Content Uniformity (BUCU) group proposed a modified approach for the evaluation of the blend and finished product content uniformity (Bergum et al., 2014a; Bergum et al., 2014b; Garcia et al., 2014). Accordingly (Garcia et al., 2014), at least 3 blend samples need to be retrieved from at least 10 locations, and a standard deviation (SD) of 3% of the target is used to determine whether 1 sample from each location or 3 samples from each location are tested. However, the group also agreed that when the sample size is small, alternative approaches may be acceptable. Therefore, a guidance for coefficient of variation (C_v), consistent with USP <905>, is followed in this work as has been done in numerous studies (Bharvada et al., 2015; Saffari et al., 2016; Yousaf et al., 2014). To characterize the blend uniformity, a precise method is important. Towards that goal, instead of using a traditional thief probe, shown to be prone to introduce sampling errors (Muzzio et al., 2003; Muzzio et al., 1997), the golden rules of sampling that suggest sampling from a moving stream of powder is employed (Venables and Wells, 2002). Consequently, amongst the tools such as the sampling riffler and process analytical technology (PAT) via near-infrared spectroscopy (NIR) (Cahyadi et al., 2014; Liew et al., 2010; Nystrom and Malmqvist, 1980), spinning riffler was used since it has the lowest sampling error (Allen, 1981).

Powder blend homogeneity carries particularly great importance for low dose tablets produced via dry mixing followed by direct compression. The topic of powder mixing has been well studied and random mixing theory is widely applied when predicting mixing homogeneity (Johnson, 1972; Lacey, 1943; Poole et al., 1964; Yalkowsky and Bolton, 1990). For instance, (Johnson, 1972) proposed that even

if the mixing were ideal, the lowest possible coefficient of variation (C_v), which is a standard measure for the quality of mixing for a random mixture, is proportional to the API particle size and inversely proportional to the drug dose. Therefore, as the dosage becomes smaller, finer drug powders are recommended and help in improving blend homogeneity (Johnson, 1972; Yalkowsky and Bolton, 1990). Unfortunately, ideal mixing of finer particles in a dry blend is a non-trivial operation and theoretical C_v values are difficult to achieve, predominantly due to fine API agglomeration. For example, (Van Der Watt et al., 1996) produced a mixture with experimental C_v values ranging from 6.09% to 8.07%, while the predicted value was 0.13%. In fact, some experimental results are in contradiction with the trend predicted from the model. As an example, (Sundell-Bredenberg and Nyström, 2001) produced uniform mixture with drug particle size ranging from 3.6 μm to 87 μm , but the trend for C_v values did not follow the expectation of lower C_v values at lower drug particle size. These differences can be attributed to API agglomeration, a phenomenon that leads to larger actual particle sizes than what is assumed in the model, or API particle size distribution effect.

A series of papers on dry mixing have carefully investigated the influence of agglomeration on predicted and actual C_v values (De Villiers, 1997; De Villiers and Van Der Watt, 1994; Garcia et al., 2004). Their work showed that the extent of agglomeration, which was estimated implicitly from dissolution data because it is difficult to directly measure the size of drug particle agglomerates in a blend or dosage form, is inversely proportional to primary drug particle size. This leads to a trend of C_v that is the reverse of what would be predicted based on primary drug particle sizes. Their work also showed that increased mixing time and/or intensity could reduce the size of agglomerates and improve C_v values. Thus, as the drug particle size becomes smaller, the existence of agglomeration caused due to strong van der Waals attraction, electrostatic charge and/or capillary forces could not only result in skewed particle size distributions, but also affect the interaction between the drug and excipients (Egermann, 1980, 1985; Huang and Ku, 2010a; Huang and Ku, 2010b; Rohrs et al., 2006; Zimmermann et al., 2004). Consequently, the agglomeration of drug particles could hinder the mixing process efficiency, resulting in poor blend uniformity (Thalberg et al., 2004). However, to date, there are no systematic investigations

that examine approaches to reduce the propensity of fine API particles to agglomerates and its effects on blend content uniformity. Common methods to break agglomerates are usually through added steps of sieving, delumping (Vanarase et al., 2013) or milling (Schenck and Plank, 2008). On the other hand, such process may lead to the fine API particles adhering to the carrier particles to produce an “interactive mixture” (Kaialy, 2016).

In this paper, a dry coating method (Jallo et al., 2012; Pfeffer et al., 2001; Yang et al., 2005), namely coating the nano-sized particles on the surface of the micronized particles, is investigated as a viable approach to reduce fine API powder cohesion, hence decreasing API agglomeration and improving mixing efficiency of dry-mixed low API dosage blends. Dry coating is a solvent-less process and may be achieved using several different devices, such as, magnetically assisted impact coater (MAIC), conical screen mill (Comil), fluid energy mill (FEM) or high-intensity vibratory mixer (LabRAM) (Han et al., 2011; Huang et al., 2015a; Jallo et al., 2012; Mullarney et al., 2011). For this work, LabRAM was selected due to its simple yet effective dry coating processing. The hypothesis that dry coating will lead to improved CU is based on mechanistic models, discussed in section 2, suggesting that creation of nano-rough surface from nearly uniform coating of silica can reduce cohesion by over an order of magnitude, leading to significant reduction in the size of agglomerates (Chen, 2008). The model indicates that although cohesion reduction is generally proportional to the inverse of guest particle size, as long as the guest size is larger than about 5 nm. In fact, the inter-particle adhesion force minimum occurs in the range 5nm to 25 nm. For further details, the reader is referred to (Chen, 2008). It is emphasized that all dry coating examples discussed here result in a uniform discrete coating layer based on the limited amount of silica used, and no film coating is formed since film coating may be detrimental to the flow (Meyer and Zimmermann, 2004). The resulting microstructure of the API in terms of agglomeration and mixedness is influenced largely by the surface properties, in particular, inter-particle forces. Specifically, the resultant adhesion force for dry coated surface modified particles is typically at least an order of magnitude smaller than that of the original uncoated particles. In addition, coating with silica nanoparticles also leads to reduced surface energy at contact. As discussed in (Han et al., 2013), hydrophilic silica M5P particle

(~20nm) coated milled Ibuprofen (5 μ m) has a decreased dispersive surface energy (37.5 mJ/m²) compared to uncoated milled Ibuprofen (54.5 mJ/m²), leading to additional reductions in adhesion force. Reduced cohesion leads to significantly reduced granular Bond number, defined as the ratio of inter-particle adhesion force to particle weight. The extent of powder agglomeration has been shown to be proportional to the granular Bond number (Castellanos, 2005). Consequently, drastic changes to cohesion after surface modification leads to over an order of magnitude reduction in Bond number. This in turn leads to a reduction in the size of API agglomerates (Castellanos, 2005) and greatly impacts blend content uniformity, which is the major novelty studied in this work. Further, the efficiency in breaking API agglomerates due to reduced cohesion may lead to better mixing efficiency via well dispersed mixing with other components in V-blender, which is also expected to help improve content uniformity for micronized powders. Overall, dry coating aids in reducing cohesion, which becomes a major driver dictating structure-property relationship relevant to this work.

Another issue of cohesive powders is that they generally exhibit tendency for tribo-charging during mixing, which further accentuates the mixing difficulties and has adverse impact on blend CU. Thus apart from cohesion based on van der Waals forces, electrostatic behavior can have great influence on achieving homogeneous blends. As shown in a recent study, there is yet another advantage of dry coating, which is the ability to reduce electrostatic charge and tribo-charging tendency (Jallo and Dave, 2015). Hence in addition to reduced cohesion, dry coating may also positively impact charge related issues. However, investigation of those aspects is outside the scope of present study. Further, the accurate feeding protocols for a small portion of materials are also important for obtaining acceptable low dose blend uniformity. For example, various methods such as periodic micro dosing are investigated which are especially beneficial for continuous manufacturing (Besenhard et al., 2016). In this work, which was performed at small batch scales, the small amount of the API is directly weighed, hence no feeding issues were encountered and are not specifically considered. Consequently, the major objective of this work is to examine how cohesion reduction of API agglomerates after dry coating with nano-sized silica particles can impact the API content uniformity in the final blend.

2. Theory

The most reliable mechanistic explanation to date for the reduction of cohesion due to the addition of flow additives is based on the work by Prof. Rumpf (Chen et al., 2009; Chen et al., 2008; Rumpf and Bull, 1990; Xie, 1997; Yang et al., 2005; Zimmermann et al., 2004). The Rumpf model suggests that the function of the guest material is to increase the distance between host particles, which may be achieved through the natural surface roughness modification of host particle by making it nano-rough (Chen et al., 2009; Chen et al., 2008; Rumpf and Bull, 1990; Xie, 1997; Yang et al., 2005; Zimmermann et al., 2004). By employing a multi-asperity contact model, (Chen et al., 2008) extended the modified Rumpf and Xie models to take into account the effect of the surface area coverage of the host particle by guest particles. Three contact forms, namely host-host, host-guest, and guest-guest are possible during contact between original host particles in the presence of nano-sized guest particles, are shown in Fig. 1. It is important to note that the degree of surface of coating can vary depending on the type of processing equipment and processing time, even when the same amount of silica particles are added as glidants. This makes the Chen model more relevant as compared to the original Rumpf model, since the latter does not account for the efficiency and extent of silica coating. Inter-particle forces are highest when host-host contacts dominate, and can be calculated by Eq. (1) (Yang et al., 2005). When there is a sparse, but uniform, guest coating, the dominant particle interaction comes from the host-guest contact, and Eq. (2) is used to calculate the inter-particle force. Eq. (3) is applied to estimate the transitional SAC from host-host to host-guest interaction (Chen et al., 2008). Guest-guest contacts dominate particle interactions when there is a dense coating of nanoparticles. The transitional SAC from host-guest to guest-guest particle interaction may be of the order of about 30% for fine spherical host particles with typical nano-silica coating (Chen et al., 2009). For that case, Eq. (4) is used to calculate the inter-particle force, but the Hamaker constant is based on the coating material instead of the host material as in Eq. (1) (Yang et al., 2005).

$$F_{ad} = \frac{A}{12} \frac{D}{2} \frac{1}{z_0^2} \quad (1)$$

$$F_{ad} = \frac{Ad}{4z_0^2} + \frac{A}{24 \left(\sqrt{\left(1 + \frac{d}{D}\right)^2 - \frac{1.21}{SAC} \left(\frac{d}{D}\right)^2} - 1 \right)^2 D} \quad (2)$$

$$SAC_{guest-host} = \frac{1.21}{1 + 2(D/d)} \times 100\% \quad (3)$$

$$F_{ad} = \frac{Ad}{24z_0^2} \quad (4)$$

In the above equations, A is Hamaker constant (material property which is a function of surface energy), d is the particle size of guest particle, z_0 is the minimum separation distance between two particles, typical value being 0.4nm (Israelachvili, 2011; John et al., 2009), and D is either the diameter (for a smooth particle) of host particle or the natural surface roughness (for rough particles, typically estimated to be about 200 nm) (Capece et al., 2014; Massimilla and Donsi, 1976; Rietema et al., 1993; Yang et al., 2005). Using these equations, the trend for adhesion force as a function of SAC is plotted as shown in Fig. 2a for the API used in this work (mAPAP) and two other powders (Ibuprofen 50 and Lactose 350). As shown, there is a sharp drop in adhesion force that begins at very low values of SAC, which marks the transition from host-host to host-guest contacts. Then there is another smaller drop, somewhat exaggerated due to the artifact of the model, when the contacts are guest-guest, occurring at 30% SAC. Although the host-host to guest-host contact transition as per Eq. (3) would occur between 0.01%-0.12% SAC for these materials, these plots indicate that for a significant reduction in adhesion, the minimum SAC should be in the range 1-10%, and for a maximum reduction, the SAC should be slightly higher than 30%. These values are in line with the recommendation from (Castellanos, 2005). Since these equations have several limiting assumptions, it may be better to target SAC higher than 30%. In

subsequent sections (3.4 and 4.1), further details are provided regarding determination of the amount of silica used.

To understand how dry coating may help in improving the blend uniformity, let us examine its effect in reducing the size of API agglomerates. For this purpose, we can apply theoretical predictions based on the relationship between the granular Bond number Bo , defined as the ratio of inter-particle adhesion force to particle weight, and the primary particle agglomeration ratio k (Castellanos, 2005).

$$Bo = \frac{F_{ad}}{mg} \approx k^{a+2} \quad (5)$$

In the above equations, F_{ad} is the adhesion force between particles obtained from Eqs. (1), (2), or (4), m is the individual particle mass, g is the gravitational acceleration, k is the ratio of aggregated particle size to the primary particle size; and a is typically the fractal dimension of the aggregates or just a power-law exponent, usually estimated to be 2.5 based on the diffusion-limited aggregation (DLA) model. In Fig. 2b, using Eqs. (1-5), estimated granular Bond number is plotted as a function of SAC. As expected, the trend for Bo is the same as that of the adhesion force shown in Fig. 2a, the granular Bond number decreases by nearly two orders of magnitude as SAC is increased. One can also estimate the size of a mAPAP agglomerate using Eq. (5), shown in Fig. 2c. As SAC increases from zero (uncoated mAPAP) to 100% via dry coating, the estimated size of one mAPAP agglomerate is reduced by about an order of magnitude. The significant effect of dry coating on blend uniformity, which was predicted by the aforementioned models, will be discussed in section 4.4. It is noted that Eq. (5) is only intended to predict the size of the primary agglomerate and as cohesion, and hence the granular Bond number. As the granular Bond number increases, larger aggregates may form due to secondary agglomeration.

In summary, the mechanism of adhesion reduction, based on the impact of surface asperities and SAC on van der Waals interactions, is quantified through Chen models and then expressed as the granular Bond number. The latter is a dimensionless parameter that provides quantitative measure of the extent of cohesion reduction after dry coating. Finally, the granular Bond number can be employed in a

mechanistic model proposed by Castellanos that allows a quantitative interpretation of the effect of the microstructure in terms of powder agglomeration, which has a direct impact on content uniformity.

3. Materials and methods

3.1 Materials

Micronized acetaminophen (mAPAP, Mallinckrodt Inc., USA) was selected as the model micronized API. Avicel PH-102 (Avicel 102, FMC Biopolymer, USA) was the excipient in the formulation. A pharma-grade hydrophobic nano-sized silica Aerosil R972P (R972P, Evonik, USA) was selected as the guest material in dry coating process or as the glidant in the mixing process.

3.2 Particle size analysis

The particle size of mAPAP and Avicel 102 was measured using a laser diffraction analysis (Rodos/Helos system, Sympatec, USA), following the procedure described in detail by (Han et al., 2013). Volume-based particle size information, an average of three repetitions, is shown in Table 1. The particle size for nano-sized R972P particle is 20nm, which was reported by the vendor.

3.3 SEM

Particle morphology and nano-coating quality were assessed by a Field Emission Scanning Electron Microscope (FESEM) (LEO 1530 170, Carl Zeiss SMT Inc., Germany). Each sample was treated with carbon coating to prevent charging before imaging.

3.4 Dry particle coating

A laboratory-scale vibratory mixing device, Resodyn acoustic mixer (LabRAM, Resodyn Corporation, USA), was used for the dry coating process. The host material (mAPAP) and a small amount of guest material (R972P) were put into a plastic jar, and processed for 5 min at intensity equivalent to 75 times gravitational acceleration. These process parameters are based on previous work (Capece et al., 2014; Huang et al., 2015b; Mullarney et al., 2011). The shearing forces generated in LabRAM resulted in collisions between particle and particle, as well as particle and wall, helping break the API agglomerates and coat the guest particles onto the surface of host particles due to strong inter-particle forces. Different

surface area coverage (SAC) coated mAPAP was prepared by adding different amounts of silica. The amount of silica required to reach a theoretical 100% SAC was calculated based on Eq. (6).

$$Gwt\% = \frac{SAC d_0^3 \rho_d}{D_0^3 \rho_D} \frac{4D_0^2}{d_0^2} \times 100\% \quad (6)$$

In the above equation, $Gwt\%$ is the silica weight percentage required to reach specific theoretical 100% SAC, D_0 is the median diameter of the host particle, d_0 is the median diameter (0.02 μm) of the guest particle as reported by Evonik Inc., ρ_D is the host particle density and ρ_d is the guest particle density (Chen, 2008). The assumptions for Eq. (6) are that all particles are spherical, all particles of the same component have the same particle size, the individual guest particles (nano-sized silica particles) are distributed evenly on the surface of host particle (mAPAP particle), and no contact deformation exists. While these are restrictive assumptions, the purpose of the equation is only to obtain a rough estimate of how much silica should be used. Actual amount of silica used in this work is determined experimentally as will be discussed in section 4.1.

3.5 Powder tester

A powder tester, Freeman powder rheometer (FT4, Freeman Technology Ltd., UK), was used to measure the packing and flowability of all powders in this study. The detailed description of test procedures can be found in (Freeman, 2007; Han et al., 2011; Huang et al., 2015b). Bulk density and unconfined yield strength (the compressed powder bed strength) were attained from bulk density and shear tests at 3kPa, respectively. Lower unconfined yield strength usually correlates with lower cohesion (Schulze, 2008). All tests were repeated 3 times. It is noted that the conditioned bulk density measured using FT4 is highly reproducible; hence although measured in triplicate, only the average value is reported.

3.6 Surface energy

The Lifshitz-van der Waals (LW) dispersive surface energy was measured by automated inverse gas chromatography (SEA-IGC; Surface Measurement Systems Ltd., UK). Five alkane probes (hexane, heptane, octane, nonane, and decane; HPLC grade, Sigma-Aldrich, USA) were utilized to determine the

dispersive surface energy according to the Schultz method (Schultz et al., 1987) at a low probe coverage of 0.5%, which means 0.5% of the sample surface sites was measured. A more detailed description of surface energy analysis used in this study can be found in (Han et al., 2013).

3.7 Preparation of low dose blends

Uncoated mAPAP or coated mAPAP was added to Avicel 102 in three different proportions to prepare 3%, 5% and 10% (w/w) API loaded blends. In addition, a mixture of uncoated mAPAP, R972P, and Avicel 102 was prepared. The mixing was done in a 4-pint V Blender (Patterson-Kelley, USA) at 25 rpm and mixing time was varied from 5 min to 90 min.

3.8 Determination of content uniformity

In this work, a spinning riffler (SP-230, Gilson company, INC., USA) was used to obtain quantitative, representative samples. First, the whole blend was divided into 16 samples, one in each of the 16 collection tubes in the sampling riffler. This was followed by further dividing a randomly chosen single sample into 16 smaller samples, where the final sample mass was greatly reduced to the desired level, i.e., ~ 300mg. Then each sample is dissolved in 100mL PH 5.8 Phosphate Buffer Solution (PBS) buffer as suggested in United States Pharmacopeia Convention, USP 29. The preparation of PBS buffer is discussed in the buffer solutions section of USP 29. Next, 3.0mL of this solution is transferred to a 25mL volumetric flask, diluted with abovementioned PBS buffer to volume, and mixed well. The amount of mAPAP in samples was measured in a UV-visible spectrophotometer (performance range: 190-1100nm, Evolution 60 S, Thermo Scientific, USA) at a wavelength of 243 nm. The beam size of this UV is around 5mm. Each sample solution is measured 3 times. The criteria for the content uniformity test of blends, which is shown in Table 2, was adapted from industrial practices and consists of two stages. First, 10 samples were utilized at Stage I. If all 10 samples achieved the drug potency average within 90-110% of the label, and coefficient of variation (C_v , defined in Eq. (7)) was smaller than 5%, the blend was considered uniform.

$$C_v = \frac{\text{standard deviation of drug content in tested samples}}{\text{average drug content in tested samples}} * 100\% \quad (7)$$

According to the criteria, if even only one sample were to be outside this range but still within 80%-120% along with C_v smaller than 6.8%, then second stage is to be considered, in which, additional 20 samples are required in the assay test. If all 30 samples obtain the average within 80%-120% along with C_v smaller than 6.8%, then the blend is considered uniform. In all other cases, the blend fails the content uniformity test.

4. Results and Discussion

4.1 Effects of silica amount on individual API powders

Selecting the right amount of silica is one of the most important parameters in dry coating based surface modification. Typically, the amount that can achieve theoretical 100% SAC is used, and is determined using Eq. (6) (Chen et al., 2008; Huang et al., 2015a). However, as discussed in section 2 (Chen et al., 2008), during the dry coating process, there are three types of contacts: API-API particle contact, nanosized silica-nanosized silica particle contact, and API-nanosized silica particle contact. Depending on the amount of silica and mixing time, different types of contacts may dominate. As shown in section 2 based on mechanistic models, a significant decrease in inter-particle force occurs when most contacts are guest-guest, i.e., nanosized silica-nanosized silica particle contacts. In addition to the mechanistic effects explained through analysis of van der Waals type contact forces in section 2, the presence of nanoparticles may also alter the surface properties such as surface energy and electrostatic charge (Han et al., 2013; Jallo and Dave, 2015; Pfeffer et al., 2001; Zimmermann et al., 2004). Accordingly, in the current and following sub-sections, the effects of using different silica amounts on the flow and packing properties of mAPAP, such as bulk density, unconfined yield strength, and dispersive surface energy are investigated. Fig. 3a shows that as silica amount increases to 0.27wt%, which corresponds to 10% SAC, the bulk density increases significantly from 0.2 g/ml to 0.39 g/ml. After that, the bulk density value reaches a plateau, regardless of further increase in the silica amount to 2.74wt%, corresponding to a theoretical 100% SAC. Similarly, for the unconfined yield strength shown in Fig. 3b,

the increase of silica amount to about 0.8wt% leads to an order of magnitude decrease in unconfined yield strength as compared to that of uncoated mAPAP. Further increasing the silica amount does not have much impact on the unconfined yield strength value. Selected dispersive surface energy results are shown for the previously mentioned materials in Fig. 3c. It may be observed that the dispersive surface energy decreases from 53.87 mJ/m² for as received mAPAP to 44.94 mJ/m² for 1wt% silica coated mAPAP, which corresponds to 36.5 % SAC. Since the surface energy is proportional to the interparticle force, the decrease correlates to lower interparticle force (Israelachvili, 2011). A slight increase is observed with 2.74wt% silica coating. Such a trend with the same silica amount is not observed in bulk density and unconfined yield strength, indicating that although surface energy is higher, the impact on the bulk property is less prominent. Overall, dry coating with silica leads to reduced cohesion and increased bulk density and use of about 1 wt %, hence theoretical SAC of a little over 30 % may be adequate, which is in line with recommendation based on the contact model (Chen et al., 2008). It is likely that use of high amounts of silica equivalent to 100 % theoretical SAC is neither necessary nor advisable. This is because too much silica may exaggerate the negative effect of inability of the dry coating device to fully break down nano-sized silica particles agglomerates. Silica deagglomeration and spreading may be improved by increased mixing time. Unfortunately, that may promote creation of a smoother coated surface, described as film coating. That would be detrimental due to the increase in inter-particle forces (Meyer and Zimmermann, 2004). The impact of the amount of silica used is further examined based on the content uniformity (CU) of blends in the next sub-section.

4.2 Effects of cohesion reduction on the content uniformity of 5% API loading blend

It is hypothesized that the reduced cohesion of mAPAP after dry coating would promote reduced agglomeration leading to improved blend uniformity. In this section, that hypothesis is tested for 5% API loaded blends and the amount of silica used for subsequent investigation is selected. The extent of API agglomeration will be examined through electron and optical microscopy as well as sieving in the next section. In Fig. 4, the experimental C_v values obtained from the assay tests are presented for 5% API

loaded blends after 20 min mixing in a V-blender. In order to better assess the improvement in CU of the blend of R972P coated mAPAP and uncoated Avicel 102, two additional blends are considered as controls: a mixture of mAPAP and Avicel 102, and a mixture of mAPAP, R972P, and Avicel 102. As seen, the blend without silica has a high C_v value of around 30%, which is much higher than the desired reference value of 5%, a result most likely due to strong agglomeration of mAPAP. The addition of R972P, which is supposed to improve the blend flowability and hence mixing quality, did not lead to any improvements, since the C_v values after adding 0.14 wt% to 2.74 wt% R972P are even higher than the blend without silica. It is likely that silica particles did not efficiently de-agglomerate mAPAP particles, but still affects the blend flowability. The C_v values are much higher than the desired reference value of 5%, meaning these two control blends fail the content uniformity test. On the other hand, for the blends with the same amount of silica when the silica particles are coated onto the surface of mAPAP particles via LabRAM, the C_v values significantly decrease. As shown, three out of the four silica dry coated API blends have smaller than 5% C_v , and all four are smaller than 6.8%. Such an improvement in mixing homogeneity is attributed to the decrease in cohesion after silica coating, which is expected due to reduced API agglomeration, hence an improved mixing process of de-agglomerated mAPAP particles and Avicel 102 particles. Since the blend mixing is done in a laboratory scale V-blender, it is hypothesized that such soft mixing process will not detach or transfer the nano-sized silica particles from the mAPAP particles. Thus, the possibility of re-agglomeration of mAPAP particles is low when coating exists. Blends with dry coated mAPAP are more likely to pass the content uniformity test when the actual potency, i.e. the actual drug content, is examined, which is considered next. For example, Fig. 5 shows drug content data for 10 samples obtained from the blend with 1wt% R972P coated mAPAP; all are within 90% and 110% of the label potency, indicating the blend is uniform. The table below the graph in Fig. 5 shows a comparison with the other two types of blends, where the maximum drug content for one sample obtained from a mixture of mAPAP and Avicel 102 can be as high as 183.56% of the theoretical value, and the C_v value is extremely high. Both are likely due to the existence of API agglomerates, as clearly explained by the maximum and minimum drug content in the table below the Figure. The

maximum drug content for mixture with silica added is even higher, a possible reason being that since both API particles and silica particles exist as agglomerates in the mixture at the very beginning, a 20 min mixing in V-blender may not have been sufficient to break these agglomerates, resulting in a heterogeneous mixture. From this comparison, it is clearly evident that the decrease in cohesion between mAPAP particles because of silica dry coating leads to reduced agglomeration, aids in mixing and promotes improved blend homogeneity. The best results are obtained for 1wt% R972P coated mAPAP blends, therefore subsequent investigations are carried out at this fixed silica amount. At this level of silica coating, the extent of API agglomeration is examined in the next section along with investigating the impact of mixing time for three different API loadings.

4.3 Effects of mixing time on blend content uniformity for three different API loadings

Apart from the cohesion of API particles, API loading and blend mixing time are also major factors that can influence blend content uniformity (De Villiers, 1997; De Villiers and Van Der Watt, 1994; Garcia et al., 2004). In the present work, the novel aspect is that dry coating with silica particles allows for reduction in cohesion and hence agglomeration as discussed in section 2, which is likely to have a significant impact on blend uniformity. Therefore, 1wt% R972P coated mAPAP blends are further investigated as a function of mixing time for three different API loadings. First, the extent of agglomeration with and without dry coating is examined using SEM and optical imaging. SEM images are shown for as received mAPAP and 1wt% R972P coated mAPAP in Fig. 6, which also shows as received Avicel 102 for the sake of completeness. Uncoated mAPAP particles, shown in Fig. 6a, illustrate agglomerates of primary particles of needle-like shapes with smooth surfaces. As Fig. 6b shows, Avicel 102 also has irregular shape, and has a much larger particle size than mAPAP. Figs. 6c and 6d indicate that after silica coating, the mAPAP particles are less agglomerated and silica particles may be seen uniformly distributed on the surface of mAPAP particles.

Although the SEM images of mAPAP particles show principal difference between uncoated and dry coated mAPAP, the nature of agglomeration is more evident in optical photographs in Fig. 7. As seen,

uncoated mAPAP has a lot more agglomerates (Fig. 7a), as compared to silica coated mAPAP (Fig. 7b). This is further examined via sieve analysis. The results in Fig. 8a show that more than 90% of uncoated mAPAP is above 125 μ m, while more than 95% of silica dry coated mAPAP is smaller than 45 μ m. Uncoated mAPAP has higher amounts retained on larger sieves due to the presence of large agglomerates, while dry coated mAPAP has fewer large agglomerates, thus higher amounts in lower size classes. The results from SEM, optical microscopy, and sieving all confirm that dry coating leads to reduced agglomeration, which should help improve the blend content uniformity. In contrast, the particle size measured using laser diffraction, which is unable to distinguish the difference between the uncoated and coated particles, is shown in Fig. 8b. This suggests that dispersion pressures as low as 0.1 bar are enough to properly de-agglomerate the large agglomerates found in uncoated mAPAP. It should also be noted that laser diffraction based particle size measurements may also be affected by the difficulties in feeding agglomerates through the small opening of the powder feeding section of this particular device.

In Fig. 9, experimentally determined C_v values are shown for 3%, 5%, and 10% API loaded blends with mixing times of 5 min to 90 min. For 10% API loaded blends, the C_v values are very low regardless of mixing time. For the lower API loading blends, the C_v values fluctuate, going from high to low and then high as mixing time is increased. It is likely that increasing the mixing time aids in breaking down of agglomerates and hence in mixing, leading to a low C_v value. However, once the blend reaches optimum homogeneity, increasing the mixing time could promote segregation, leading to a higher C_v value. The average values of the drug content of 10 samples along with their standard deviations for each mixing time for all three blends are shown in Figs. 10a through 10c. For each API loading, the mixing times that resulted in acceptable range of potencies are shown within a dashed box. By combining both the C_v values (Fig. 9) and drug content values of 10 samples (Fig. 10), it is observed that for 3% and 5% API loading, blends for three mixing times could achieve desired homogeneity. For 10% API loading, all mixing times considered could achieve desired homogeneity. These results indicate that it is easier to achieve homogeneity for higher API loaded blends, which is in line with the theoretical models (Johnson,

1972; Yalkowsky and Bolton, 1990), which predict that theoretical C_v values are inversely proportional to the drug dose. Overall, from these results, 30 min mixing time would have been sufficient for all three API loaded blends with dry coated API to obtain desired blend uniformity. In Fig. 11, SEM images are shown for these blends after 30 min mixing. Although this is rather subjective, it appears that an interactive mixture is evident for 10% API loaded blend, although that is not the case for the other two API loadings. This may also explain the better homogeneity achieved for 10% API loading blend since interactive mixtures obtain better homogeneity than random mixtures (Hersey, 1975).

In order to assess the impact of silica dry coating of the API, drug content and uniformity for 30 min mixing time are evaluated for the two other types of blends considered as controls in earlier sections. These are blends without silica and those with 1wt% silica amount added. These results are presented in Table 3 along with those for the blends with dry coated mAPAP. The blends without silica have C_v values of 85.43%, 49.99%, and 49.39% for API loadings of 3%, 5% and 10 % respectively, which are much higher than the desired value of 5%. These improve to some extent for silica added blends, having C_v values of 36.35%, 47.53%, and 19.83% for 3%, 5% and 10% API loaded blends, respectively. These smaller values as compared to corresponding blends without silica indicate that the presence of silica aids in overall mixing when blends are mixed for 30 minutes. For dry coated mAPAP blends, C_v values are 3.8%, 3.04% and 1.54% for 3%, 5% and 10% API loading blends, respectively. Hence, dry coating leads to significantly reduced C_v values and these results demonstrate that only blends with coated mAPAP could reach the desired homogeneity. Without API dry coating, much longer mixing times may be necessary to promote improved mixing that may provide lower C_v values (Malmqvist and Nystrom, 1984).

4.4 Models for Predicting C_v Values

There are several excellent papers presenting review and discussion of the models for predicting theoretical C_v values based on the drug dosage, API particle size, and API particle size distribution

(Huang and Ku, 2010a; Huang and Ku, 2010b; Rohrs et al., 2006). For example, Johnson et al. derived models from statistical calculations to estimate the C_v by assuming ideal mixing of two components (Johnson, 1972). If it is single sized particle, Eq. (8) is used for the calculation.

$$C_v = 100 \times \left(\frac{\pi \times \rho \times d^3}{6 \times G \times 10^{-3}} \right)^{\frac{1}{2}} \quad (8)$$

If the particle size distribution follows a binomial distribution, two cases are derived:

- i) Up to 1% drug loading, Eq. (9) is used for the calculation:

$$C_v = 100 \times \left(\frac{\pi \times \rho}{6 \times G \times 10^{-3}} \right)^{\frac{1}{2}} \times \left[\sum f_i (d_i \times 10^{-4})^3 \right]^{\frac{1}{2}} \quad (9)$$

- ii) For 1-10% drug loading, Eq. (10) is used for calculation:

$$C_v = 100 \times y \times \left(\frac{\pi \times \rho}{6 \times G \times 10^{-3}} \right)^{\frac{1}{2}} \times \left[\sum f_i (d_i \times 10^{-4})^3 \right]^{\frac{1}{2}} \quad (10)$$

$$\sum f_i = 1 \quad (11)$$

In the above equations, C_v is the coefficient of variation of the dose (%), d is the mean particle size (μm), y is the fraction of major component in the mixture, ρ is density of the drug (g/ml), G is the drug dose per sample (mg), f_i is the weight fraction of mean particle size d_i (μm).

The Johnson model (Johnson, 1972) shows that for a random mixture, C_v is proportional to the API particle size, and inversely proportional to the drug dose. The results shown in the previous section including Table 3 are in general agreement with that. Let us consider using Johnson's model to estimate expected C_v values for all three cases of dry coated mAPAP API Loadings. For this purpose, theoretical predictions based on the relationship between the granular Bond number Bo and the agglomeration ratio k discussed in section 2 are employed (Castellanos, 2005). Based on that discussion and equations (1-5), as well as known properties, the agglomeration ratio for dry coated mAPAP is 2.28, indicating a median

agglomerated particle size about 25 μm based on the volume averaged particle size. Likewise, the agglomeration ratio for uncoated mAPAP is 10.38, indicating a median agglomerated particle size about 114 μm based on the volume averaged particle size. On the other hand, actual experimental value of an average agglomerate size may be estimated from sieve data and may be more relevant. Based on the sieve data, the average particle size for dry coated mAPAP is 31.25 μm , calculated from the summation of multiplication of weight percentage in each sieve range and the average sieve size of upper and lower sieve, which is not very different from the Bond number based theoretical prediction. Similarly, the average particle size for uncoated mAPAP based on sieve size is 761.6 μm , which is much higher than the theoretically predicted value. As mentioned in section 2, when the granular Bond number is very high, there is a greater chance of secondary agglomeration and this may partially explain this discrepancy. Using the average particle size from sieve data as estimates of actual agglomerate sizes, C_v values can be estimated using the Johnson model for both uncoated and dry coated mAPAP blends. These values are listed in Table 4 along with the experimental results duplicated there for the sake of comparison. As seen in Table 4, the use of just the average particle size results in theoretical C_v values are much lower than the experimental values. This means that the effect of particle size distribution needs to be considered, which can also be done using the Johnson model. Using the sieving based PSD in the Johnson model predicted C_v values are computed and shown in Table 4, indicating that the PSD data provides much closer values to the experimental results. For example, C_v values of 1.73%, 1.31% and 0.88% for 3%, 5% and 10% dry coated API loadings, respectively. As a reference, Johnson model is also used based on the full PSD data available from laser diffraction, which failed to show difference between uncoated and dry coated. Those results are also included in Table 4. All the results shown in Table 4 demonstrate that the reduced agglomeration after dry coating leads to improved content uniformity and both actual and predicted results show the extent of improvement due to dry coating. Also, the primary API size cannot be used to predict or explain the experimental C_v values.

Considering API agglomeration leads to dramatic under prediction of blend C_v values, a brief recap of the popular models for predicting theoretical C_v values based on the drug dosage and API particle size distributions is warranted. In (Yalkowsky and Bolton, 1990) model, although no experimental results were provided, the assumption was that mixing is homogeneous and the particle size follows a log-normal distribution. Later Rohr et al. extended the model to a more widely used geometric values (Yalkowsky and Bolton, 1990; Rohrs et al., 2006), along with experimental validation. Subsequently, Huang and Ku (Huang and Ku, 2010a; Huang and Ku, 2010b) developed models taking the effect of PSD skewness into account, which are still based on the assumption that the particle size distribution is log-normal distribution. These models are expected to predict C_v values accurately, as long as API agglomeration is not significant and the PSD related parameters required may be easily obtained. However, these models may need to be further extended to capture the effect of the agglomerated API particle size distribution. Unfortunately, in their present form they are not useful as shown in this work since the detailed PSD of the fine API before and after dry coating, other than sieve data, is not available. Further, they also require that the PSD follows log-normal distribution. Hence one cannot utilize currently available advanced models that account for the width or skewness of the particle size distribution (Huang and Ku, 2010a; Huang and Ku, 2010b). To make matters worse, the actual state of agglomeration within the blend cannot be determined just based on the API sieving. In summary, the analysis presented here is intended to show that the API agglomeration has a major impact on the content uniformity and existing models cannot be used if the extent of agglomeration is not measurable, as indicated by very low predicted C_v values when laser diffraction PSD, which does not account for agglomeration, is used. This work also shows that API dry coating significantly mitigates the adverse impact of agglomeration on the blend content uniformity.

5. Conclusions

The cohesion reduction via dry coating, as expected based on theoretical considerations from section 2, is shown to lead to improved drug content uniformity for 3 %, 5 %, and 10 % fine API loaded

blends. Approximately 1 wt% silica, which equates to 36.5% SAC after dry coating, was sufficient to achieve improved content uniformity in pharmaceutical blends. Blend mixing time of 30 minutes led to acceptable content uniformity for all blends having dry coated API. The C_v values of the blends with dry coated mAPAP were significantly lower as compared with two control blends, namely those without silica and those with silica added during blending. Experimental C_v values for 3%, 5% and 10% dry coated API loaded blends were 3.8%, 3.04% and 1.54%, respectively, which are comparable to their corresponding theoretical values derived from the Johnson model using sieve-based PSD. In contrast, experimental C_v values for 3%, 5% and 10% API loaded blends with silica were 36.4%, 47.5% and 19.8%, respectively, and were significantly higher than their corresponding theoretical values derived from the Johnson model using sieve-based PSD. The discrepancies between the predictive models and experimental results, along with very large granular Bond numbers for uncoated mAPAP, suggest the presence of secondary agglomeration in the API. This phenomenon is not captured in presently available predictive models, and the results of this work highlight the need for improvement of the aforementioned predictive models. In conclusion, cohesion reduction by dry coating is a promising approach to improve the content uniformity of cohesive API blends.

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(a) host-host contact

(b) guest-host contact

(c) guest-guest contact

Fig. 1. Type of contacts: (a) host-host contact, (b) guest-host contact, and (c) guest-guest contact. Adapted from (Chen et al., 2009).

(a)

(b)

(c)

Fig. 2. Interparticle adhesion, granular Bond number and agglomeration ratio for mAPAP, Ibuprofen 50, and Lactose 350 as a function of surface area coverage (SAC). The median particle size of mAPAP, Ibuprofen 50 and Lactose 350 which was used for these calculations are 11 μm , 61 μm and 26 μm respectively. (a) Interparticle adhesion, (b) granular Bond number, and (c) agglomeration ratio.

(b)

(c)

Fig.3. (a) Bulk Density, (b) Unconfined Yield Strength, and (c) LW dispersive surface energy (values above the bar represent theoretical surface area coverage) for mAPAP as a function of silica amount

Fig.4. Coefficient of variation (C_v) as a function of silica amount for three types of 5% API loaded blends after mixing for 20 min, namely (mAPAP+Avicel 102), (mAPAP+R972P+Avicel 102), (dry coated mAPAP+Avicel 102)

t=20 min	mean(%)	minimum(%)	maximum(%)	C _v (%)	n
mAPAP+Avicel 102	119.31	81.40	183.56	29.98	10
mAPAP+1% R972P+Avicel 102	137.78	60.47	245.15	50.37	10
Coated mAPAP+Avicel 102	96.62	90	107.13	5.13	10

Fig.5. Drug content data for 10 samples of 5% silica dry coated API loaded blends, prepared by 20 minute mixing in V-blender. Data in the accompanying table also displays drug contents for 5% API loaded blends without silica, and 5% API loaded blends with silica added

(a) Uncoated mAPAP

(b) Avicel 102

(c) Coated mAPAP

(d) Coated mAPAP

Fig.6. SEM images of (a) uncoated mAPAP, (b) uncoated Avicel 102, (c) and (d) coated mAPAP with 1% R972P

(a) Uncoated mAPAP

(b) Coated mAPAP

Fig.7. Pictures of (a) uncoated mAPAP, (b) coated mAPAP

(a)

(b)

Fig.8. Results of (a) particle size from sieve analysis, and (b) volume-based particle size distribution for uncoated mAPAP and coated mAPAP with 1wt% R972P

(Data for Fig.8a, see Supplemental Material, Supplemental Table 1)

Fig.9. C_v values as a function of mixing time for 3%, 5%, and 10% API loading blend with coated mAPAP (1wt% R972P)

(a)

(b)

(c)

Fig.10. Drug content of 10 samples for (a) 3%, (b) 5%, and (c) 10% API loading

(e) 3% API loading

(f) 5% API loading

(g) 10% API loading

Fig.11. SEM images of (e) 3%, (f) 5%, and (g) 10% API loading blend with coated mAPAP with 1wt% R972P after 30 min mixing

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Table 1

Particle size and true density of raw materials

Material	Particle size (µm)			⁴True density ρ (g/mL)
	¹D10	²D50	³D90	
Micronized APAP	2	10.98	37	1.29
Avicel 102	32	122	244	1.58
R972P	-	0.02	-	2.65

1: 10% of particles are smaller than this value

2: 50% of particles are smaller than this value

3: 90% of particles are smaller than this value

4: Reported by each manufacturer

Table 2

Industry criteria to pass content uniformity test

Testing	Blends
Stage I Test 10	Pass if: All drug contents within 90-110% of drug label value and $C_v < 5\%$
Stage II Test additional 20	Pass if, for all 30 units: Only 1 sample has drug content outside 90-110% of drug label value, No sample has drug content outside 80%-120% of drug label value and $C_v < 6.8\%$

Table 3

Drug content data for mixing time of 30min at different API loadings for three types of blends: no silica, silica blended, and silica dry coated

Data analyzed	3% API loading			5% API loading			10% API loading		
	no silica	silica added	silica coated	no silica	silica added	silica coated	no silica	silica added	silica coated
Average Drug Content (% of label value)	94.84	71.95	97.85	91.55	119.90	95.37	92.45	92.56	93.78
C _v (%)	85.43	36.35	3.80	49.99	47.53	3.04	49.39	19.83	1.54
Minimum Drug Content (% of label value)	50.82	37.82	91.62	59.97	55.48	90.53	37.95	68.63	90.64
Maximum Drug Content (% of label value)	387.10	141.44	103.57	254.39	259.42	99.73	189.17	131.91	96.20

No silica: Micronized Acetaminophen (mAPAP) + Avicel PH102

Silica added: mAPAP + R972P + Avicel PH102

Silica dry coated: Dry coated mAPAP + Avicel PH102

Table 4

Predicted C_v values for uncoated and dry coated mAPAP blends based on laser diffraction or sieve particle size used in the Johnson model

API Loading	Experimental C _v (%)	Predicted Cv based on laser diffraction data (Uncoated API)(%)		Predicted Cv based on sieve data (Uncoated API)(%)		Experimental C _v (%)	Predicted Cv based on laser diffraction data (Dry coated API)(%)		Predicted Cv based on sieve data (Dry coated API)(%)	
		Johnson -Mean	Johnson- PSD	Johnson- Mean	Johnson-PSD		Johnson- Mean	Johnson-PSD	Johnson-Mean	Johnson-PSD
3%	85.4	0.03	0.14	18.21	33.77	3.8	0.03	0.14	0.15	1.73
5%	50.0	0.02	0.11	14.10	25.62	3.04	0.02	0.11	0.12	1.31
10%	49.4	0.02	0.07	9.97	17.16	1.54	0.02	0.07	0.08	0.88

Reduced API cohesion after dry coating

More efficient mixing

Reduced agglomerate size

Improved Blend Uniformity

5% API loading blend (t= 20 min)

CU of 5 wt % blend greatly improved for API dry coated with 1 wt % silica