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Macro- and micro-mixing of a cohesive pharmaceutical powder during scale up

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ABSTRACT

Efficient powder mixing involves a macro and micro mixing mechanism, achieved by a combination of various types of mixers. Selection of the mixer is based on the understanding of the cohesiveness of the components in the mixture. In the current study, a cohesive active pharmaceutical ingredient (API), X, was used as the model compound to study the effectiveness of convective mixing in a bin blender and intensive shear mixing with a comil (conical mill). Convective mixing in the bin blender only delivered limited macro mixing for API X and the resulting blend was heterogeneous at both micro and macro scales. After blending in the bin blender, the comilling process added micro level mixing by introducing locally intensive mechanical shear. The resulting blend showed improved homogeneity at the micro scale, but was still heterogeneous at the macro scale. An additional mixing step in the bin blender after comilling was required to ensure the uniformity of the mixture at both micro and macro scales. The significance of the second convective mixing to micro mixing was underscored at commercial scale manufacture as compared to the development scale. Despite the scale dependency on the comilling step, the extensive shear exerted during the comilling step facilitated further micro mixing by the convective mixing in the second bin mixing step. The investigation demonstrates that a rational selection of mixing steps with various types of mixers is crucial to achieve both macro and micro mixing of cohesive materials from development to commercial scales.

1. Introduction

Mixing of powders is a common yet important process that is used to achieve uniform mixtures in food, chemical, and pharmaceutical indus tries. It is especially critical in pharmaceuticals as accurate dosing is vital to efficacy and safety in patients. The criticality of homogeneity is evidenced by the strict requirements for dose uniformity from regulatory agencies around the world. As a result, mixing of pharmaceutical pow ders, typically cohesive by nature, is extensively studied in various types of mixing equipment to understand mixing mechanism via convection, diffusion or shearing [1 4]. While these studies have accu mulated mechanistic understanding of the particular types of mixing equipment, few investigations have studied the effect of combining different types of mixers to blend cohesive materials. Homogeneity of pharmaceutical powder normally requires multiple mixing mechanisms to be involved [5], which is difficult to achieve with one type of mixer.

Our study demonstrates that the combination of different types of mixers is a practical and effective means to achieve uniform distribution of cohesive materials, such as APIs. The key to the uniform distribution is to enable both macro and micro mixing to reach uniformity at both scales. It is achieved by engaging different mixing mechanisms in the process, such as convective and shear mixing. Both convective and shear mixing can deliver macro and micro mixing depending on the cohesiveness of the material. Macro mixing occurs at the bulk level via dispersion, and is fast, while micro mixing occurs at the particle level via shearing or diffusion. Although convective mixing in a bin blender is an efficient way to achieve macro scale uniformity, our study suggests that macro scale uniformity in a bin blender is not achievable for API X without substantially engaging micro scale mixing via the intensive shear mechanism in a comil first. Although comilling is typically used as a size reduction method [6,7], we emphasized more on the shear mixing function of comilling in this study. Recent studies have shown that comilling is an effective way of distributing minor ingredients onto various pharmaceutical powders [8,9]. Only after the comilling step delivers some degree of micro uniformity can mixing in a bin blender further convey both micro and macro uniformity and result in uniform distribution of API X across the powder bed. Such

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mechanism was only revealed at commercial scale manufacture but not apparently at the development scale.

2. Material and methods

A proprietary formulation containing Microcrystalline Cellulose, Lactose Anhydrous, Crospovidone, silicon dioxide, magnesium streareate and API X was used in the study.

API X was micronized to less than 30 μm (100% by a light scattering method). The API has a true density of 1.3 g/ml and is needle like in shape. API X was loaded at concentrations for 1.25%, 2.5%, or 5% w/w. The batch size in the study ranged from 20 kg to 750 kg. All materials were loaded in a bin blender, mixed at 12 rpm for 108 revolutions (blend 1) and passed through a comil. The mixture passing through the comil (blend 2) was received in a second bin blender and then fur ther mixed at 12 rpm for 120 revolutions (blend 3). Samples were taken at the top or bottom of the powder bed after each mixing step for the 20 kg scale batches in a 68 L bin blender. The schematic process dia gram and sampling locations are shown in Fig. 1. Due to the large batch size, additional sample locations were added for a 300 kg batch in a 900 L bin blender and a 750 kg batch in a 2000 L bin blender as shown in Fig. 2. Samples were tested for uniformity and concentration by High performance liquid chromatography (HPLC). While a Quadro® U10 comil with a milling chamber diameter of 127 mm was used for the 20 kg batch, a Quadro® 196S comil with a milling chamber diameter of 305 mm was used for the 300 kg and 750 kg batches.

The following metrics were used to characterize the homogeneity of the blends:

1) The maximum difference (*MD*) in the average potency of API X among samples taken from multiple locations of the powder bed from the same process step, which is shown in Eq. (1)

$$MD \quad Max(\overline{X_i}) - Min(\overline{X_i}) \tag{1}$$

where $\overline{X_i}$ is the average potency at a specific location *i*. If samples are taken only from the top and bottom of the bin blender (68 L),

$$MD \quad |\overline{X_T} - \overline{X_B}| \tag{2}$$

where $\overline{X_T}$ and $\overline{X_B}$ stand for the average potency of the sample from the top and bottom of the bin blender, respectively. *MD* indicates the macro mixing behavior and is expected to be close to zero for effective macro mixing.

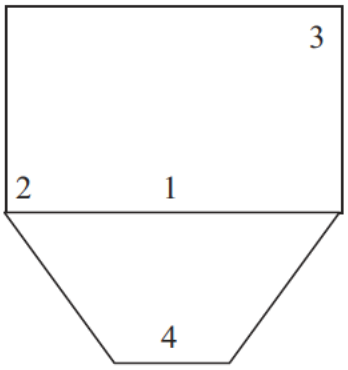


Fig. 2. Sampling locations in the 900-L or 2000-L bin.

2) The relative standard deviation of potency measurements within a sample, or RSD_S, as is shown in Eq. (3),

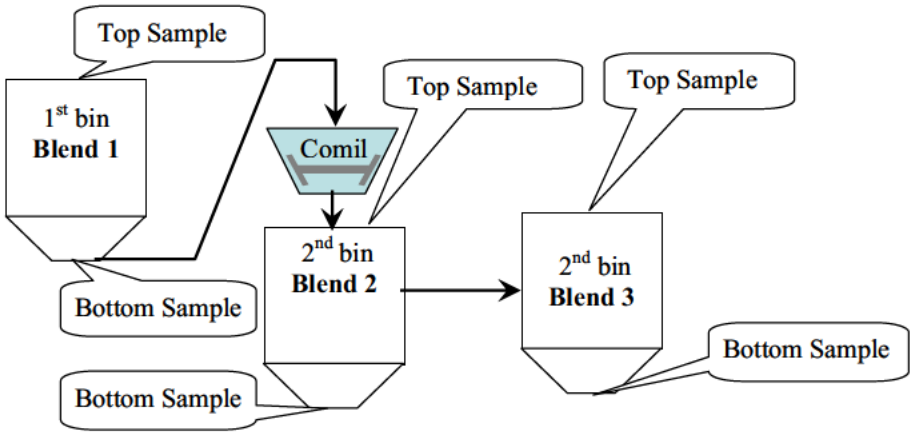
$$RSD_S \quad \sqrt{\frac{\sum_{j\ 1}^{n}\left(X_{ij}-\overline{X_i}\right)^2}{n-1}}\Big/\overline{X_i} \tag{3}$$

where *n* is the number of potency measurements within a sample, X_{ij} is an individual observation of potency at a specific location *i*. RSD_S is an indicator of micro mixing behavior at a specific location with a low RSD_S suggesting a uniform distribution of API X in the vicinity of that sampling location.

3) The relative standard deviation for potency measurements from all samples within a particular mixing step, or RSD_m, which is shown in Eq. (4),

$$RSD_m \quad \sqrt{\frac{\sum_{i\ 1}^{k}\sum_{j\ 1}^{n}\left(X_{ij}-\overline{X_m}\right)^2}{N-1}}\Big/\overline{X_m} \tag{4}$$

where *k* is the number of sampling locations, *N* is the total number of potency measurements across all samples from a particular mixing step ($N = k * n$), and $\overline{X_m}$ is the observed mean of all these individual measurements in the mixing step. RSD_m represents the overall mixing behavior of a specific mixing step. A powder mixture that is well mixed at the micro and macro scales yields a low RSD_m value while



heterogeneity at either micro or macro scale results in a high RSD_m value.

3. Results and discussion

Fig. 3 presents the MDs of three 20 kg batches in a 68 L bin blender at each step of mixing with 1.25%, 2.5% and 5% w/w of API X, respectively. The MD between the two samples after the first bin mixing step was substantial (24.3% 83.5%). However, it decreased dramatically after the comilling step (9.5% 17.1%) and was further narrowed after the second bin mixing step (3.2% 6.2%). Such drops in MDs clearly suggested that regardless of the target concentration of API X in the batch, macro mixing in the first bin mixing step was ineffective, and macro uniformity still relied on subsequent steps, i.e., comilling and the second bin mixing step.

The drop in MD is accompanied with the improving micro uniformity through the mixing process that is evidenced by the declining RSD_S as shown in Fig. 4. Blend 1 was heterogeneous at the micro scale with RSD_S between 18.9% and 39.3% across the three batches, in line with the macro heterogeneity shown in MDs. In contrast, blends 2 and 3 were homogeneous at the micro scale (RSD_S of <4.7%), regardless of sampling location and target concentration of API X. This suggests that uniformity at the micro scale was attained via the extensive local shear exerted during the comilling step. There was no improvement in micro scale homogeneity between blends 2 and 3, suggesting that maximum micro mixing was achieved at the comilling step and the second blending step did not extend micro mixing further.

Therefore, regardless of the drug load, blend 1 is heterogeneous across the powder mixture, blend 2 is micro scale homogenous but macro scale heterogeneous, and blend 3 is homogenous across the powder mixture. In terms of function of the mixing steps, the first mixing step in the bin blender delivers coarse macro mixing only with no micro mixing, the comilling step delivers micro mixing with limited macro mixing, and the second mixing step in the bin blender is a macro mixing step.

The increase in homogeneity at both macro and micro scales across the mixing steps also was evidenced by declining RSD_m as illustrated in Fig. 5. The RSD_m started at as high as 43.9% for blend 1 and ended at less than 3.5% for blend 3. The trend is similar across the three concentrations in the study.

Upon scale up at 300 kg or 750 kg, the mixing of the API X performed differently from the 20 kg scale. Fig. 6 shows the maximum difference in potency across the mixing steps at 300 kg and 750 kg with the 5% w/w drug load and the 20 kg scale batch at 5% w/w is plotted in the same graph for comparison. Blend 1 had a smaller MD at commercial scales (<20%), suggesting improved yet still ineffective macro mixing upon scale up. This distinction between scales on blend 1 indicates that macro mixing in the first blending step is more effective at larger scales due to increased shear provided upon scale up [10].

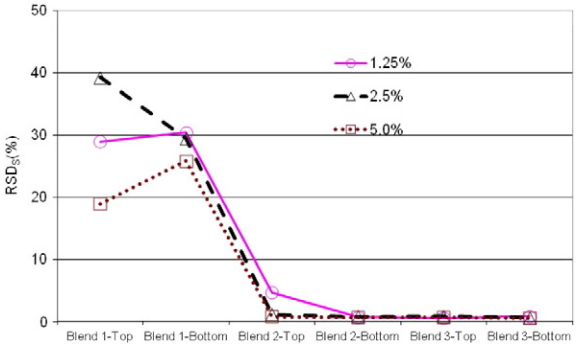


Fig. 4. Within-sample uniformity of blend through the process (20 kg).

The MD dropped slightly from blend 1 to blend 2 for both 300 and 750 kg batches, unlike the larger decrease observed at the 20 kg batches. This distinction between scales suggests that comilling at the larger scale had much less impact on macro mixing due to more effective macro mixing that occurred in the preceding bin mixing step. On the other hand, MD for blend 3 dropped significantly to 1.8% (300 kg) and 1.4% (750 kg), similar to that from the 20 kg batches. This is an indicator that macro mixing in the second bin blender at the development scale was as sufficient as that at the commercial scale.

The RSD_S of the 300 kg and 700 kg batches from each step of mixing are plotted in Figs. 7 and 8, respectively. Although there is a decrease in RSD_S from blend 1 to blend 2 at each sampling location in the powder bed, the degree of micro scale mixing in the comilling step at large scales is not as effective as that observed at the 20 kg scale. This is demonstrated by the wide range of *RSDs* observed for blend 2 after comilling, i.e., 2.7% 10.5% for the 300 kg scale and 4.8% 15.1% for the 750 kg scale. The corresponding range on the three 20 kg scale batches is much narrower, 0.8% 4.7%. The noticeable impact from scale up in micro scale mixing delivered by comilling is likely due to the change in the size of the comil causing a difference in the residence time and working volume of the powder in the chamber.

Despite the less efficient micro scale mixing with the comil, the local shear exerted through comilling still disrupts the cohesive bonds between API X particles, facilitating the micro scale mixing in the second blender. *RSDs* of blend 3 for the 300 kg and 750 kg batches decrease to less than 1.9% and 1.7%, respectively, implying that sufficient micro scale uniformity was achieved. These values are similar to that of the 20 kg batches. As there was no discernable decrease in *RSDs* for the 20 kg batches from blend 2 to blend 3, such decrease in *RSDs* upon scale up strongly indicates that the second mixing in the bin blender plays a crucial role in scale up, i.e., continuing the micro mixing that was initiated by the comilling step.

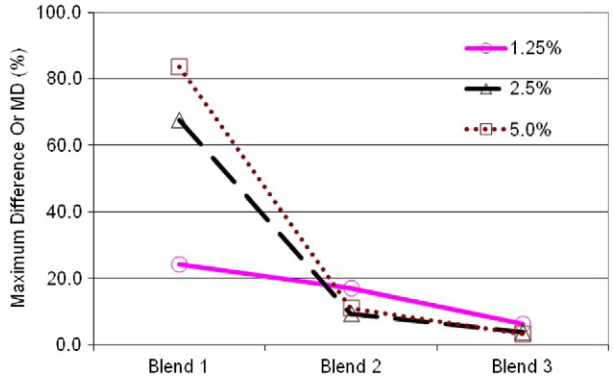
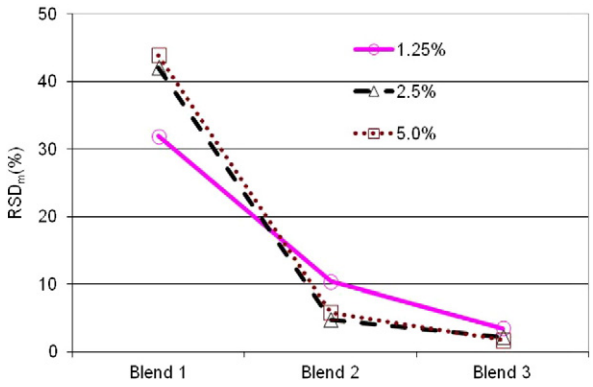


Fig. 3. Decrease in maximum difference (MD) of mean potency throughout the process



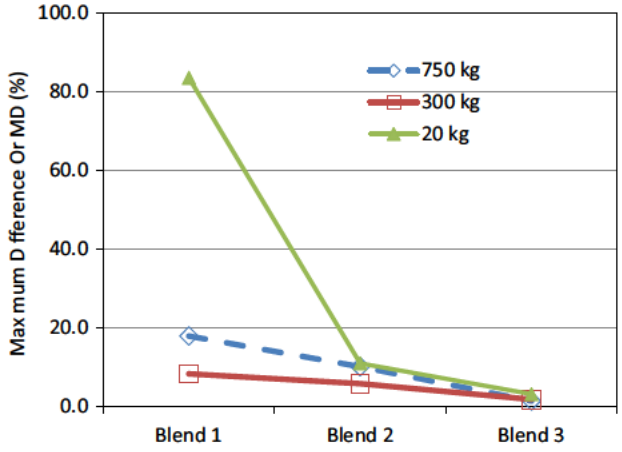


Fig. 6. Decrease in maximum difference (MD) of mean potency (5% API).

It is clear that the second mixing step in the bin blender involves both micro scale mixing and macro scale mixing. The effect of this mixing step on micro scale mixing is not obvious at a smaller scale, because the preceding comilling step is sufficient to achieve the required micro scale mixing for uniformity and, therefore, any further micro scale mixing is negligible. When the comilling step delivers insufficient micro mixing upon scale up, the micro mixing function of the second bin mixing step becomes apparent.

The detailed mechanism of mixing upon scale up is not revealed through RSD_m as it lumps effect from both macro and micro scale mixing mechanisms in one index. The decrease in RSD_m could have two drastically different starting points from blend 2, i.e., blend 2 is not uniform at one scale but is uniform at the other scale, or it is not uniform at either micro or macro scales, as suggested by RSD_s. Nevertheless, RSD_m is a direct indicator of the overall homogeneity as shown in Fig. 9. The slight difference between the two commercial scale batches is likely due to sampling, while more heterogeneity of blend 1 at the development scale reflects less effective shear mixing in the first blending step compared to that at the commercial scale.

Additionally, the effective macro and micro mixing achieved at the second mixing step is likely associated with the coating effect at the particle level exerted from the proceeding coming step [8,9]. SEM images of pure API and blends, as shown in Fig. 10, demonstrate that the needle like API covers the surface of the excipients, allowing the excipients functioning as API carrier. Since the mixing of API coated excipients is driven by the excipients and is less dependent on the cohesiveness of API, the uniformity of API in the second bin blending step is more readily achieved than that in the first bin blending step.

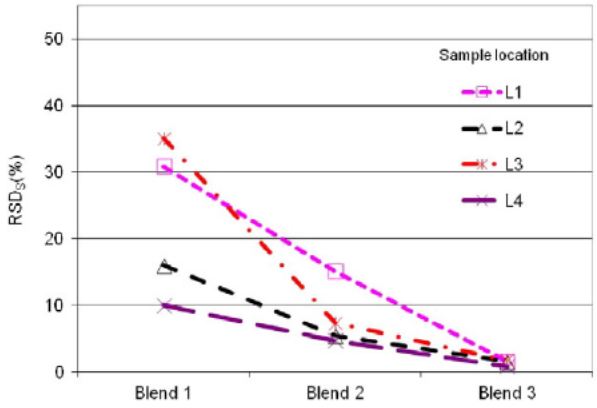


Fig. 8. Within-sample uniformity of blend through the process (750 kg).

In summary, the second mixing step in the bin blender introduces additional micro scale mixing beyond its macro mixing role due to the coating effect from the comilling step. This hidden role in micro scale mixing is crucial in the uniformity of API X at commercial scales. Fig. 11 summarizes the mixing mechanisms involved in the mixing process for API X.

4. Conclusion

The current investigation revealed that the mechanism of mixing cohesive materials in a bin blender changes with bin size. With smaller bins, convective mixing occurs only at the macro scale. Commercial scale bins introduce a component of micro scale mixing due to the increased shear provided by the higher drop heights.

Although the effectiveness of micro scale mixing in a comil depends on the equipment and batch size, a subsequent convective mixing in a bin blender removes such dependency by continuing the micro mixing concurrently with macro mixing. These findings indicate that a combination of micro and macro scale mixing mechanism is required for homogeneous mixing of cohesive materials.

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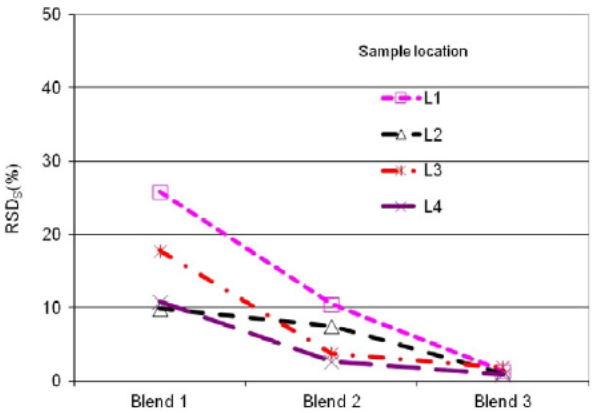

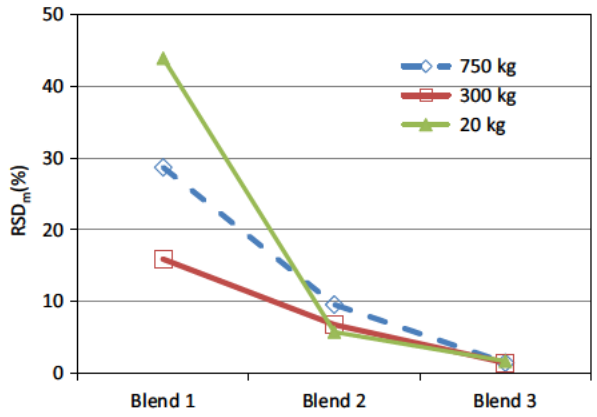

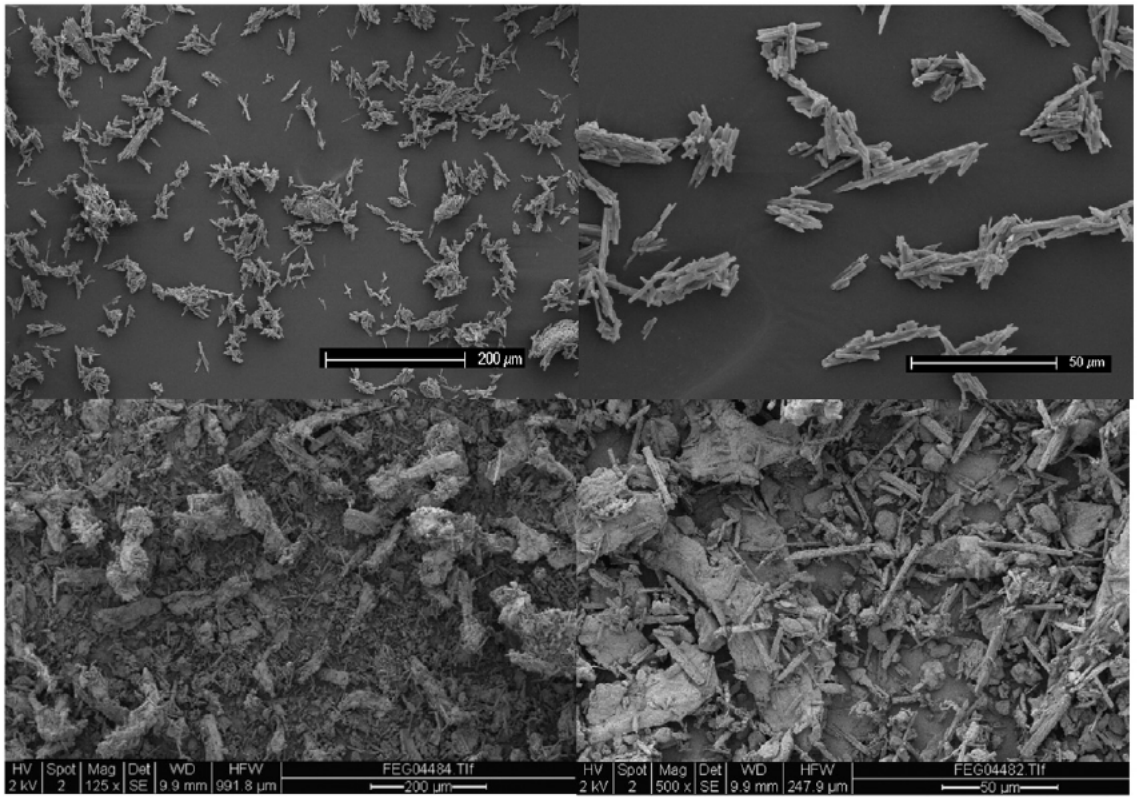

Fig. 10. Coating of excipients by API. Top figures: needlelike pure API; Bottom figures: blend 2 showing coating of excipient by needle like API.

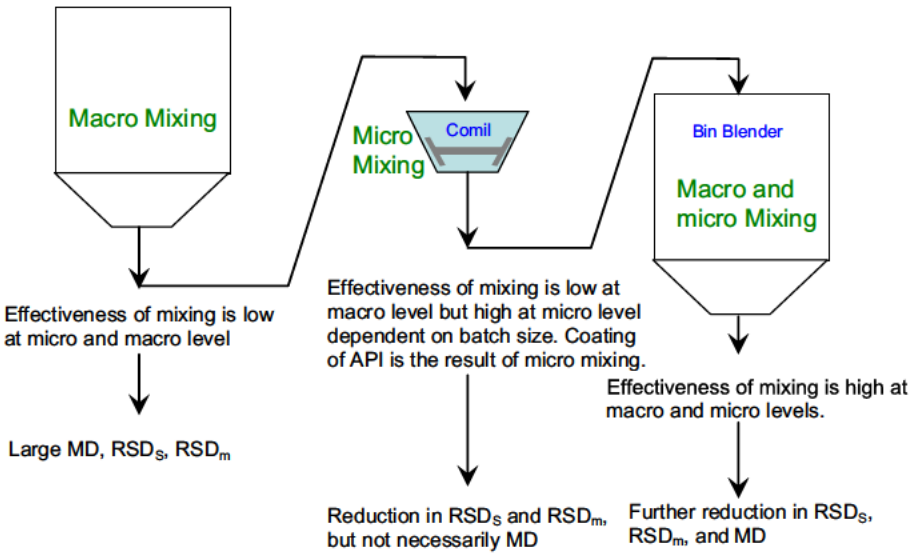

Fig. 11. Schematic mixing mechanism of API X.

References

[1] B. Chaudhuri, A. Mehrotra, F.J. Muzzio, M.S. Tomassone, Cohesive effects in powder mixing in a tumbling blender, Powder Technol. 165 (2006) 105–114.
[2] J.J. McCarthy, Micro-modeling of cohesive mixing processes, Powder Technol. 138 (2003) 63–67.
[3] A. Alexander, O. Sudah, P. Arratia, N. Duong, S. Reynolds, F.J. Muzzio, Characterization of the performance of bin blenders part 3 of 3: cohesive powders, Pharm. Technol. 28 (2004) 54–74.
[4] N. Harnby, An engineering view of pharmaceutical powder mixing, Pharm. Sci. Technol. 3 (2000) 303–309.
[5] M. Poux, P. Fayolle, J. Bertrand, Powder mixing: some practical rules applied to agitated systems, Powder Technol. 68 (1991) 213–234.
[6] L.R. Schenck, R.V. Plank, Impact milling of pharmaceutical agglomerates in the wet
[7] M. Llusa, K. Sturm, O. Sudah, H. Stamato, D.J. Goldfarb, H. Ramachandruni, S. Hammond, M.R. Smith, F.J. Muzzio, Effect of high shear blending protocols and blender parameters on the degree of API agglomeration in solid formulations, Ind. Eng. Chem. Res. 48 (2009) 93–101.
[8] Q. Zhou, L. Shi, W. Marinaro, Q. Lu, C.C. Sun, Improving manufacturability of an ibuprofen powder blend by surface coating with silica nanoparticles, Powder Technol. 249 (2013) 290–296.
[9] M.P. Mullarney, L.E. Beach, R.N. Davé, B.A. Langdon, M. Polizzi, D.O. Blackwood, Applying dry powder coatings to pharmaceutical powders using a comil for improving powder flow and bulk density, Powder Technol. 212 (2011) 397–402.
[10] F.J. Muzzio, A.W. Alexander, Scale up of powder-blending operations, Pharm. Technol. 29 (2005) 34–42.