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RESEARCH PAPER

Mixing of Cohesive Pharmaceutical Formulations in Tote (Bin) Blenders

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ABSTRACT

Experiments were conducted to determine the influence of process parameters such as fill level, mixing time, shear, and baffle presence along with material attributes such as initial active aggregate size and concentration on the homogeneity of a cohesive placebo formulation in a pilot plant scale tote blender. The formulation was a ternary system made up of microcrystalline cellulose, NaCl or KCl salt, and magnesium stearate. Blend homogeneity was evaluated by sampling the blend using core samplers. Salt concentration was quantified using a conductivity technique. After a brief transient mixture, homogeneity became insensitive to mixing time and initial active concentration, however, it was a strong function of fill capacity and initial active aggregate size. Sixty percent fill was found to be optimum. Active aggregate size had an adverse effect on mixture homogeneity. The best results were obtained when the salt aggregates were initially comparable in size to that of the excipient and a high shear pre-blending step was implemented prior to dilution in the tote blender. For the strongly agglomerating material examined here, pre-blending was only beneficial if the initial aggregate size was relatively small. For cohesive systems that form large and rigid aggregates, it is recommended to mill or screen the potentially agglomerating component and then mix the system in a blender equipped with an intensifier bar.

Key Words: *Agglomeration; High shear mixing; Pharmaceutical blending; Powder mixing; Pre-blending; Sampling; Tote blender*

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INTRODUCTION

The mixing of particles in the dry solid state is one of the oldest industrial processes known to man. Since prehistoric times, it has been necessary to manually mix grains of various sizes to produce foodstuffs, building materials, cosmetics, and medicine to mention but a few. The need for such products has grown tremendously over time. Advances in science and technology have enhanced the quantity and quality demands on granular blends. Currently, particle blending is a key step in most industrial processes, especially in the manufacture of pharmaceuticals, where 80% of drug products are sold as solid dosage forms (tablets and capsules) and subject to stringent Food and Drug Administration (FDA) regulations on content uniformity.

According to PhRMA (Pharmaceutical Research and Manufacturers of America), the FDA approved 370 new medicines in the 1990s, up from 239 during the previous decade, and it is estimated that the pharmaceutical industry in the United States alone invested $22.5 billion in R&D during the year 2000.[1] Recent advances in medicine, biology, and biochemistry, resulting in the discovery of extremely potent compounds, are driving the FDA to raise the standard for the quality of drugs. On the other hand, the aging populations of the developed world are generating an increasing pressure for lower drug costs. This stresses the need for more efficient manufacturing and handling practices, especially in the area of powder processing.

Previous investigations on the mixing of cohesive powders, in general, and pharmaceutical materials, in particular, have been limited. General reviews on the mixing of solid particles discussing basic principles regarding homogeneity assessment, sampling techniques, and blender types can be found.[2–4] Although scarce, work focusing on the mixing of pharmaceutical formulations dates back to 1962, when Kaufman[5] mixed penicillin G and dihydrostreptomycin sulfate in a double cone and V tumbling blenders at various fill levels. Kaufman observed that: (i) the V blender performed slightly better than the double cone; (ii) larger V blenders mix faster than smaller ones; (iii) active concentration did not affect homogeneity of mixture; and (iv) after 250 revolutions the mixing index became erratic. However, since the statistics were based on only 10 samples per experiment obtained using thief samplers, these results might be affected by substantial experimental error.

Later, Orr et al.[6] conducted a broad investigation on the effects of cohesion, particle size, and concentration of fine calcium carbonate (minor component) on the homogeneity of free-flowing and cohesive lactose mixtures in the Y and Lodige Morton mixers. An end-sampling thief was used to collect all the samples. It was observed that while free-flowing mixtures mixed faster than cohesive ones, cohesive mixtures were able to reach a greater degree of homogeneity. As the minor component concentration increased, the time needed for the mixture to reach the lowest attainable concentration increased. However, the time it took the concentration fluctuation to stabilize (below 0.8% change) decreased. Cohesive material became agglomerated, and the breaking of such agglomerates was the rate-determining step in high dilution mixing. Breaking up agglomerates is much slower than the randomized mixing of the component itself. The Lodige Morton blender, equipped with shearing blades, performed better than the Y tumbling blender due to its ability to overcome the tensile strength of the cohesive agglomerating mixture.

A substantial fraction of earlier studies on tumbling blenders utilized sub-optimal sampling and analysis techniques, generating potentially inaccurate information.[7,8] Sampling error was seldom addressed in previous work, where accurate sampling was simply taken for granted. A review of previous sampling work, along with the introduction of a ''core sampler'' (an improved sampling tool), was presented by Sudah et al.[9] Recent work by Muzzio et al.[10] demonstrated the applicability of such an improved powder sampler in characterizing the degree of mixing of free-flowing materials in tote blenders as a function of fill percentage, mixing time, baffling, and initial loading.

Cohesive powders differ from free-flowing ones in the magnitude of their inter-particle forces (mechanical, electrostatic, Van der Waals, and surface tension).[6] Such forces are greatly influenced by physical properties of the particles such as size, shape, surface morphology, and compressibility, causing the material to exhibit variable flow characteristics.[11] Castellanos et al.[12,13] recently studied the flow dynamics of fine cohesive powders in rotating drums and found that cohesion forces are dominant and ambient gas plays an important role, especially for particles smaller than 30 μm. Granular material was found to exhibit four flow regimes: plastic, inertial, fluidized, and entrained. The authors

constructed a phase diagram where particle size determined the flow regime as a function of velocity. Free-flowing material tends to go from the plastic to the inertial regime as velocity increases, while fine cohesive powders with a 10–100 μm size range can evolve from a plastic regime to a fluidized one, and then to an entrained flow regime as velocity increases. The materials used in this study exhibited partial fluidization,[12] especially in the flowing topmost layer, while the core layer remained in the plastic regime, causing non-uniform consolidation of the powder bed.

As previously mentioned, agglomeration of cohesive powders slows down the dispersion process and is often a hindrance to achieving localized homogeneity (efficient micromixing). Humidity is a major factor in the formation of agglomerates due to liquid bridging.[14,15] Abouzeid et al.[14] conducted an extensive study of the effects of humidity on the mixing of free-flowing quartz particles in a small horizontal drum (10″ length; 2″ inner diameter). The authors found that at low humidity [<30% relative humidity (RH)], electrostatic charging occurred, with particles sticking to the blender walls, while at high humidity aggregates formed. Intermediate humidity (30%–50%) was recommended, where the results were most reproducible. Furthermore, it was observed that the dynamic angle of repose increased at low RH as particles stuck to the wall (static charging), increasing the lifting of the material; and also at high RH, where they formed stronger inter-particle bonds due to liquid bridging. The authors obtained faster mixing at low and high RH due to larger velocity gradients, however, mixing was found not to be a function of time after 500 revolutions.

De Villiers[16] focused on drug particle agglomerates for cohesive pharmaceutical mixtures. He found that fine powders (~30 μm) adhered to larger free-flowing ones, forming aggregates that could cause mixing and handling problems. The author extended a first-order model typically used in mixing studies to describe the breakdown of agglomerates as a combination of erosion and abrasion mechanisms, where the aggregate size decreased exponentially with mixing time until reaching a plateau. It was concluded that mixer speed and presence of internal moving parts (shear) increased the rate of agglomerate breakdown. Abrasion (breakaway of small particles due to interaction with mixture or walls) was found to be the rate-limiting process. An effective final agglomerate size independent of mixer speed, type, and initial agglomerate size was reached (plateau in deagglomeration curve), where further reduction in size became impractical.

Other studies investigated the effect of impeller speed on granule formation. Knight et al.[17] varied the impeller speed from 450 to 1500 rpm ($24 < \text{Froude} < 270$) in a high shear vertical mixer to granulate calcium carbonate powder mixed with polyethylene glycol binder liquid. The initial bimodal size distribution of agglomerates approached a unimodal profile at long mixing times. At 450 rpm, spherical agglomerates were produced. At 800 rpm, slightly deformed agglomerates were observed, and at 1500 rpm, smaller sized agglomerates were generated due to breakage. Furthermore, Vromans et al.[18] found that in the granulation of a multicomponent steroid hormone mixture, very high impeller speeds led to demixing. It was speculated that in granulation processes that have initially different sized agglomerates, impellers preferentially destroy weaker agglomerates composed of larger particles, leading to poor content uniformity.

Effects of important process parameters such as fill level, mixing time, initial agglomerate size, and shear on the degree of blend homogeneity are examined. Unlike the previous study, this pharmaceutical blend is a ternary cohesive mixture with the excipient, active, and lubricant particles being considerably different in size, shape, and cohesion, rendering it a realistic placebo formulation. In this work, we use the same accurate sampling technique described earlier,[9] supplemented with an efficient analysis method, to characterize the mixing of cohesive pharmaceutical formulations in a pilot plant 2-cubic-feet (56-L) Gallay tote blender.

This article is organized as follows: The material and methods section describes the experimental set-up and materials, and defines the experimental procedures employed to obtain mixing data. The results and discussion section presents the experimental results along with any observed phenomena. Finally, the conclusions section provides an interpretation of the presented results along with recommendations.

MATERIALS AND METHODS

Apparatus and Materials

Blending experiments reported in this study were performed in a pilot scale 2-cubic-foot (56-L) tote blender (GEA Gallay Systems Ltd.,

Table 1

Summary of Physical Properties of the Material

Components	Microcrystalline Cellulose (MCC PH-102)	KCl (Granular)	NaCl[a] (Micro-milled)	Magnesium Stearate
Proportion (wt%)				
Formulation 1	96%	3%		1%
Formulation 2	68%	30%		2%
Formulation 3	96%		3%	1%
Mean particle size (μm)	100	360	94 (<180 μm) 360 (<595 μm)	11
Bulk density (g/mL)	0.33	1.1	0.47	0.11

[a]NaCl was sifted to generate particles $< 180\,\mu m$ and $< 595\,\mu m$.

Birmingham, UK), described in detail in Ref. [9]. The material used in this investigation consisted of a placebo pharmaceutical blend composed of microcrystalline cellulose (Comprecel™, Mingtai Chemical Co., Ltd., Taiwan), NaCl (New Metron Impex Inc., Ontario, Canada) or KCl (Morton Salt™, Morton Int. Inc., Chicago, IL), and magnesium stearate (Mallinckrodt Inc., St. Louis, MO). Salt was chosen as a simulated active ingredient for three reasons: first, it is commonly used in formulations to improve dissolution of drug and bioavailability;[19] second, it is rather simple to detect and quantify in samples; and third, KCl is an actual active used in sodium replacement formulations. As for the other two components, microcrystalline cellulose (Comprecel PH-102) was selected since it is one of the leading excipients used in real formulations[20] (third ranked worldwide), while magnesium stearate is used in 86% of all solid dose formulations.[20] The formulation ingredients' properties are listed in Table 1.

Experimental Method

Two different sizes of salt were used to investigate the effects of active aggregate size on the degree of mixing: micronized NaCl and granular KCl and NaCl. The KCl was sieved below 595 μm, while the NaCl was sieved either below 180 μm or below 595 μm, as indicated in Table 1. The salt was used in two ways. In the first method, it was pre-blended with a portion[†] of the excipient in a high shear mixer and then diluted and lubricated (adding magnesium stearate) in the tote to the desired concentration, a method previously employed by Samyn and Murthy.[21] The second method was to directly blend all components in the tote blender, where they were initially poured through a hopper with the excipient loaded first, followed by the salt, with the magnesium stearate added last. In order to investigate the effects of active concentration on homogeneity, two salt concentrations were used, 3% and 30% by weight, in three formulations. One formulation had 96% microcrystalline cellulose, 3% KCl, 1% magnesium stearate; the second had 96% microcrystalline cellulose, 3% NaCl, 1% magnesium stearate; and the third had 68% microcrystalline cellulose, 30% KCl, 2% magnesium stearate. For the sake of brevity, the formulations having 3% KCl, 30% KCl, and 3% NaCl will now be referred to as Formulation 1, Formulation 2, and Formulation 3, respectively. The rate of mixer rotation was held constant at 10 rpm for all the experiments performed.

The experiments were conducted in a humidity-controlled chamber where the RH was set at 25% in order to minimize moisture uptake by the hygroscopic salt. Materials were also stored in the low humidity environment prior to the experiment. Salt can uptake significant moisture in less than 10 min when the RH is changed from single-digit values to 33% RH,[19] hence it is practically difficult to maintain controlled environmental conditions throughout the manufacturing process at large scales.

The following parameters were also varied from experiment to experiment: fill level, mixing time,

[†]Portion represents approximately 25% and 17% of the excipient for 40% fill and 60% fill levels, respectively.

Table 2

Experimental Grid Showing All the Experiments Discussed in This Article

	Number of Mixer Revolutions			
	20% Fill	40% Fill	60% Fill	80% Fill
Formulation 1[a]				
No Baffle		4, 8, 16, 32, 64, 128		
Baffle	2, 4, 8, 16, 32, 64, 128	4, 8, 16, 32, 64, 128	4, 8, 16, 32, 64, 128	4, 8, 16, 32, 64, 128
Pre-blend		4, 8, 16, 32, 64, 128	4, 8, 16, 32, 64, 128	
Formulation 2[b]				
No Baffle				
Baffle		4, 8, 16, 32, 64, 128	4, 8, 16, 32, 64, 128	
Pre-blend		4, 8, 16, 32, 64, 128	4, 8, 16, 32, 64, 128	
Formulation 3[c]				
No Baffle ($< 595\,\mu m$)		4, 8, 16, 32, 64, 128	4, 8, 16, 32, 64, 128	
No Baffle ($< 180\,\mu m$)		4, 8, 16, 32, 64, 128	4, 8, 16, 32, 64, 128	
Pre-blend		8, 16, 32, 64, 128	4, 8, 16, 32, 64, 128	

[a]Formulation 1, 96% microcrystalline cellulose, 3% KCl, 1% magnesium stearate.
[b]Formulation 2, 68% microcrystalline cellulose, 30% KCl, 2% magnesium stearate.
[c]Formulation 3, 96% microcrystalline cellulose, 3% NaCl, 1% magnesium stearate.

and whether a baffle was present. Table 2 illustrates the experimental grid examined in this article. All the experiments were sampled using the core sampling method discussed in Ref. [9]. The analysis technique was as follows: the amount of salt in each sample was quantified by dissolving the sample in a constant amount of deionized water (45 mL) and the ionic strength of the solution was measured using a conductivity probe. The conductivity technique was an inexpensive, speedy, and reliable method, being sensitive only to the presence of salt. Microcrystalline cellulose and magnesium stearate are hydrophobic, have negligible dissolution in water, and have no effect on conductivity measurements.

RESULTS AND DISCUSSION

The rate of mixing in tumbling blenders has been established to be a strong function of fill level for free-flowing materials.[9,22] This observation was also confirmed for cohesive mixtures, as illustrated in Fig. 1, where the RSD (relative standard deviation) of Formulation 1 is plotted against the number of revolutions for 80%, 60%, 40%, and 20% fills with a baffle (closed symbols), and 40% fill without a baffle (open symbols). In all cases, fill percentage represents percentage of total vessel volume occupied by untapped powder. Similar to the free-flowing case,[9] the mixing rate (logarithmic slope of the mixing curve) with respect to time was slowest at high fill levels (80%), and increased as the fill percentage decreased, becoming nearly independent of fill at low loading (20%). Unlike the free-flowing situation, there is no cascading layer for cohesive powders; instead, there is a failure region at the surface of the material, which slips when the shear stress increases.[12,13] This failure region increases as the fill decreases due to a greater volume of air available to fluidize the bed and increase its dynamic angle of repose.[12] However, at very low fill level (20%), sliding of the powder bed along the blender walls diminished the rate of material turnover, as evidenced by the 20% fill mixing curve mixing slower than the 40% fill mixing curve. Comparing the mixing curves for the 40% fill baffled and unbaffled cases, it was apparent that, as in the free-flowing case, the presence of the prism-shaped baffle[9] recommended by the manufacturer enhanced the mixing rate only moderately.

Contrary to the free-flowing scenario, the mixing curves in Fig. 1 do not display a monotonic decrease in RSD. Rather, the curves reach a minimum RSD above 10% before they begin to climb again (as noted in Ref. [14] as well). The bumps in the mixing curves at short times (16 revolutions) are artifacts caused by slow material turnover, which

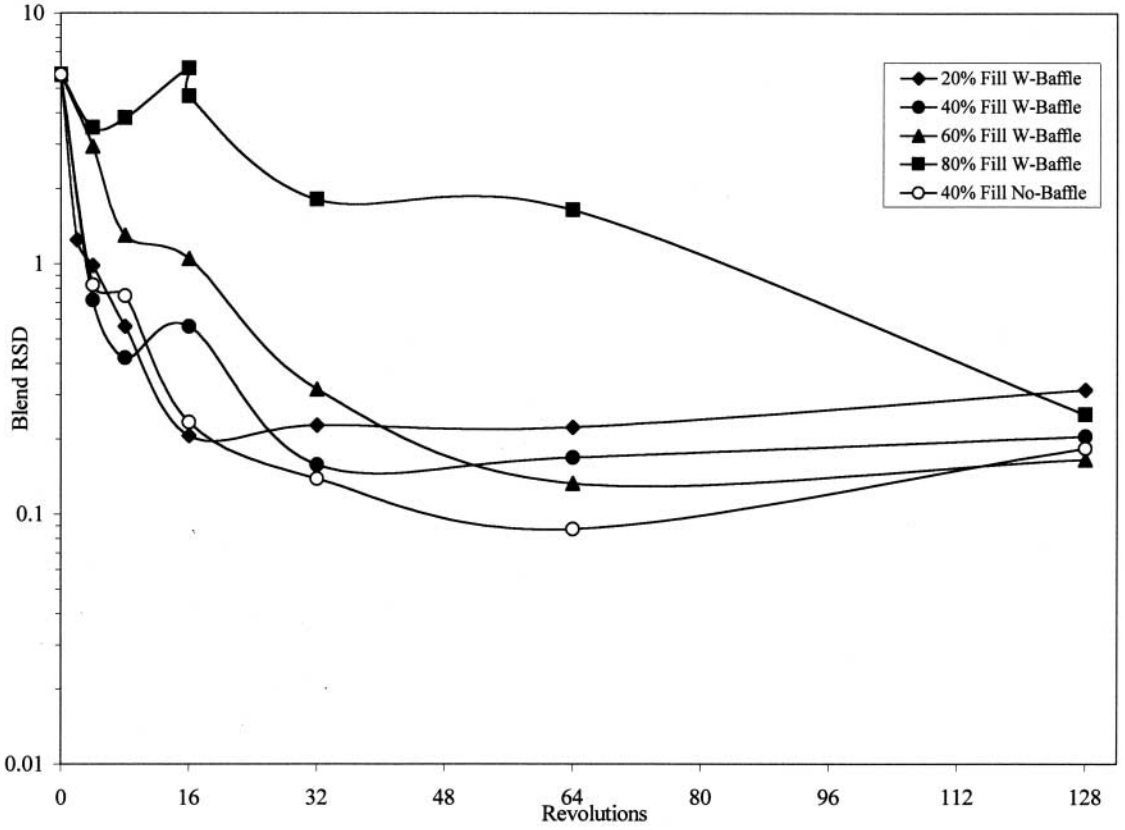

Figure 1. Mixing curves for Formulation 1. The RSD is plotted vs. the number of revolutions at 10 rpm for cases employing a baffle at fill levels equal to 20% (closed diamond), 40% (closed circle), 60% (closed triangle), 80% (closed square), and without a baffle at 40% (open circle).

was exacerbated in the 80% fill case where the experiment was repeated and the spike in the RSD at 16 revolutions occurred reproducibly. The salt was initially loaded in the center of the blender through a hopper. After eitght revolutions, the salt dispersed enough to cover an area accessible to the core samplers, where most of the samples were low in salt. This is shown in Fig. 2a, where the KCl concentration frequency for Formulation 1, 80% fill case at four revolutions displays that nearly all the samples were low in KCl with an average sample concentration of 2.78% KCl. At 16 revolutions, the 40% fill, 60% fill, and 80% fill mixing curves displayed a spike in the RSD, meaning that the salt had regrouped in the blender (central region), resulting in a greater number of highly concentrated KCl samples and thus elevating the RSD of the mixing batch. In Fig. 2b, which displays the frequency for Formulation 1, 80% fill case at 16 revolutions, there are noticeably more concentrated KCl samples than in Fig. 2a (four revolutions); the average is no longer close to 3%, it is 9.17% KCl. In Fig. 2c, the concentration frequency for Formulation 1, 80% fill at 128 revolutions is no longer highly skewed as in the previous two plots, rather it has an approximately gaussian shape with a mean sample concentration of 2.87% KCl and a much narrower spread. All of this indicates that at short times, the material mostly mixes in the radial direction in the center of the blender, and there is an inherent turnover time for this loading pattern (16 revolutions) after which axial mixing becomes a factor in distributing the powder in the axial direction.

The increase in the RSD of the curves at longer times was attributed to size segregation caused by the large size difference between the KCl salt and the rest of the components (360 μm vs. 100 μm and 11 μm). Although the microcrystalline cellulose and the

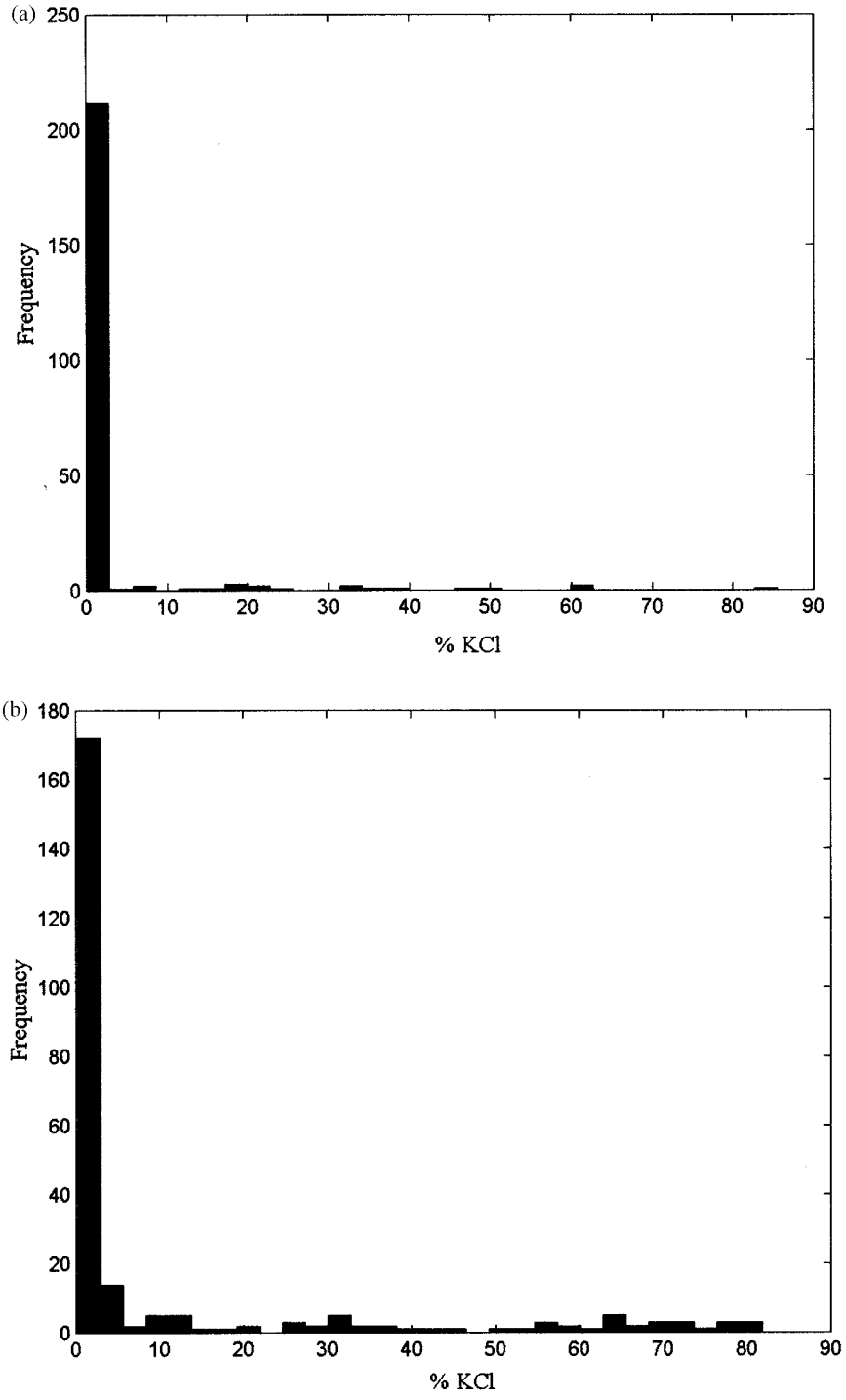

Figure 2. Frequency distribution of sample KCl concentration for Formulation 1 at 80% fill. (a) Distribution at four revolutions with the measured mean concentration of KCl equaling 2.78%. (b) Distribution at 16 revolutions with the measured mean concentration of KCl equaling 9.17%. (c) Distribution at 128 revolutions with the measured mean concentration of KCl equaling 2.87%.

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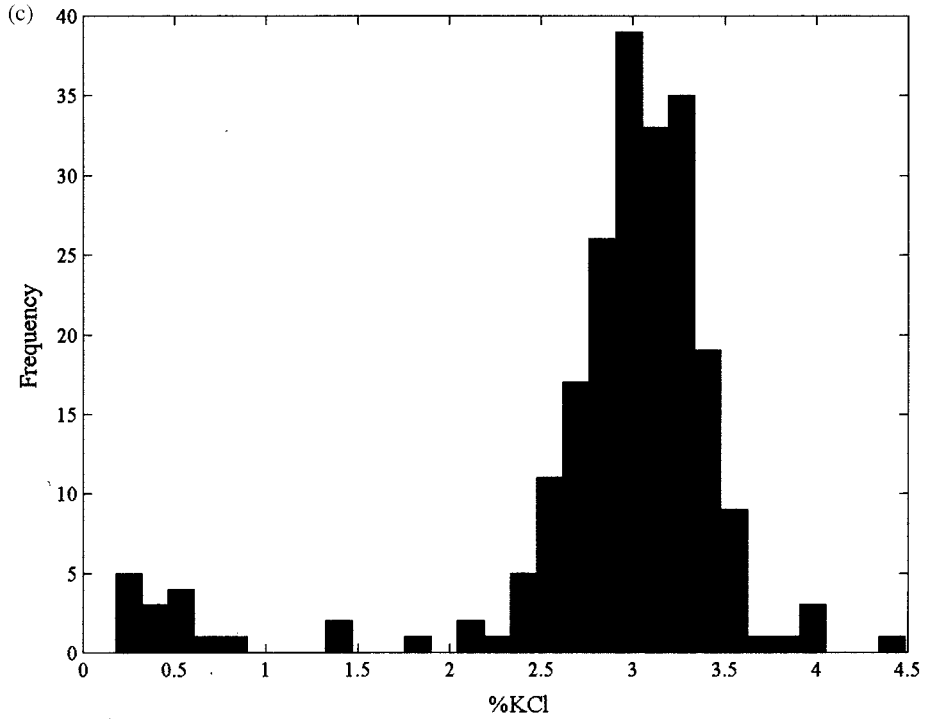

Figure 2. Continued.

magnesium stearate may have coated the coarse salt, this did not result in the perfectly homogeneous "structured" or "ordered" mixture that had been proposed in the literature.[23] As the particles get coated they increase in size even further, and may bind to other coarse particles (to be discussed shortly); instead of becoming fully dispersed in the mixture, the particles size-segregate, resulting in an unacceptably high RSD value well above 5%.

Effect of Active Concentration

Figure 3 illustrates the effects of varying the concentration of the active component from 3% to 30% by weight. The RSD is plotted as a function of time for Formulation 1 and Formulation 2, respectively, for 40% and 60% fill capacities. The initial scale of segregation for Formulation 2 (30% KCl) is lower than that for Formulation 1 (3% KCl), hence the higher RSD value at time zero. Both sets of curves show identical trends, with the 40% fill mixing slightly faster than the 60% fill. Comparing both formulations, it is apparent that the mixing rate for the two formulations is similar, with Formulation 2 (30% KCl) yielding slightly faster rates. This may be attributed to the larger fraction of free-flowing material, however, the improvement in mixing was not substantial.

Effect of Active Aggregate Size

The aggregate size of the active ingredient has an important effect on the rate of mixing and on the ultimate homogeneity of the powder mixture. Figure 4 displays the RSD as a function of the number of revolutions at 40% and 60% fill capacities for two variations of Formulation 3. The first variation was made using micronized NaCl sieved below 180 μm (initial mean aggregate size 94 μm), and the second was made with coarser NaCl sieved below 595 μm (initial mean aggregate size 360 μm). It is apparent that there is an appreciable difference in the mixing curves for the two variations. The variation having the smaller NaCl aggregates mixed faster and attained a greater degree of homogeneity than the large-aggregate NaCl blend. It was also evident that the effect of fill percentage was reduced as the active aggregate size decreased, as evidenced

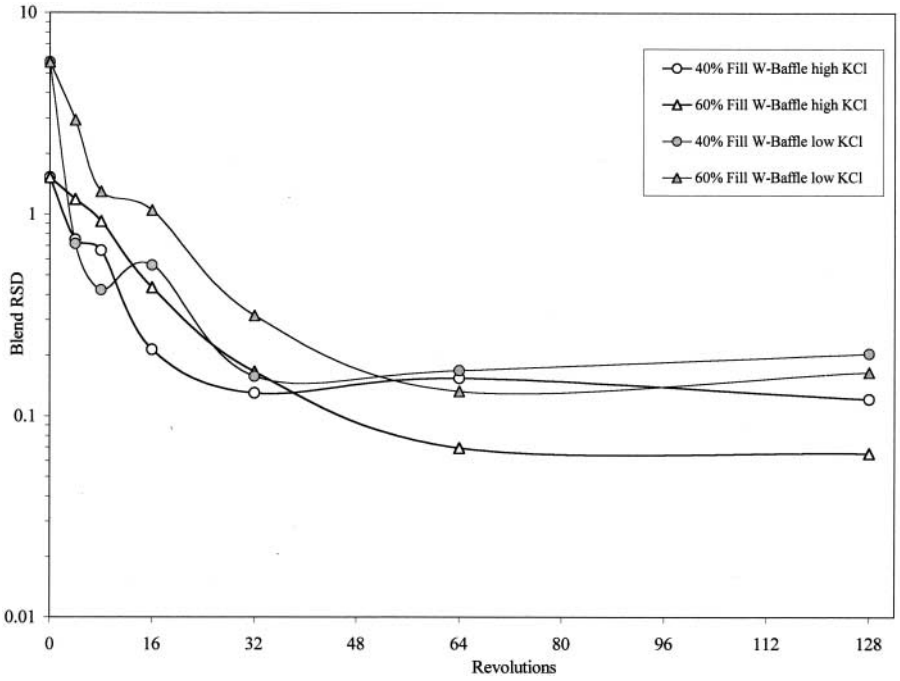

Figure 3. Comparison between the mixing curves of low (3%) and high (30%) active KCl blends. The RSD is plotted vs. the number of revolutions at 10 rpm for baffled 40% (circle) and 60% (triangle) fill levels for Formulation 1 (closed symbols) and Formulation 2 (open symbols).

when the 40% and 60% fill mixing curves for both formulation cases were compared. As the mean aggregate size decreased, the different components of the blend became closer in size and began to approach the trend of the free-flowing case,[9] where the difference between 40% and 60% fill capacities is negligible.

Although the micronized NaCl had a mean aggregate size of 94 μm, comparable in size to the rest of the components, the RSD reached a plateau and remained well above the acceptable limit of 5%. This was due to the salt's ability to sequester moisture[19] from the other components to form large aggregates, which amounts to a reversal of the dispersion process. As shown in Fig. 5, sieving the discharge of a 40% fill Formulation 3 experiment after 32 revolutions proved the presence of such large salt agglomerates. The clumps shown in Fig. 5 were rather large in size, with the largest clumps being approximately 2 cm in diameter and nearly pure in salt. Such situations are often encountered in industry, where agglomerates in large bins, as large as tennis balls, are sometimes observed. While care was taken to work in a low RH environment, it was difficult to dehumidify the bulk excipient to the point where the salt would not agglomerate.

High Shear Pre-blending

Harding et al.[24] proposed that the kinetic energy of mixing was more important than the duration of mixing for the homogeneity of cohesive powder blends. Higher kinetic energy input can be achieved in powder mixers if they are equipped with internal moving parts imparting a greater amount of shear on the material. Some studies[6,16,21,25] investigated blenders equipped with internal moving paddles and blades to mix powders. They found that high shear mixers (with internal moving parts) out-performed purely tumbling blenders in terms of the final homogeneity of the mixture. Other factors such as mixer speed and initial agglomerate size were found to also have a noteworthy influence on homogeneity.[16]

Since retrofitting a pilot plant tumbler such as the tote blender used in this investigation is expensive and highly impractical, pre-blending the active with a portion of the excipient in a high shear V blender equipped with an intensifier bar appeared to be a

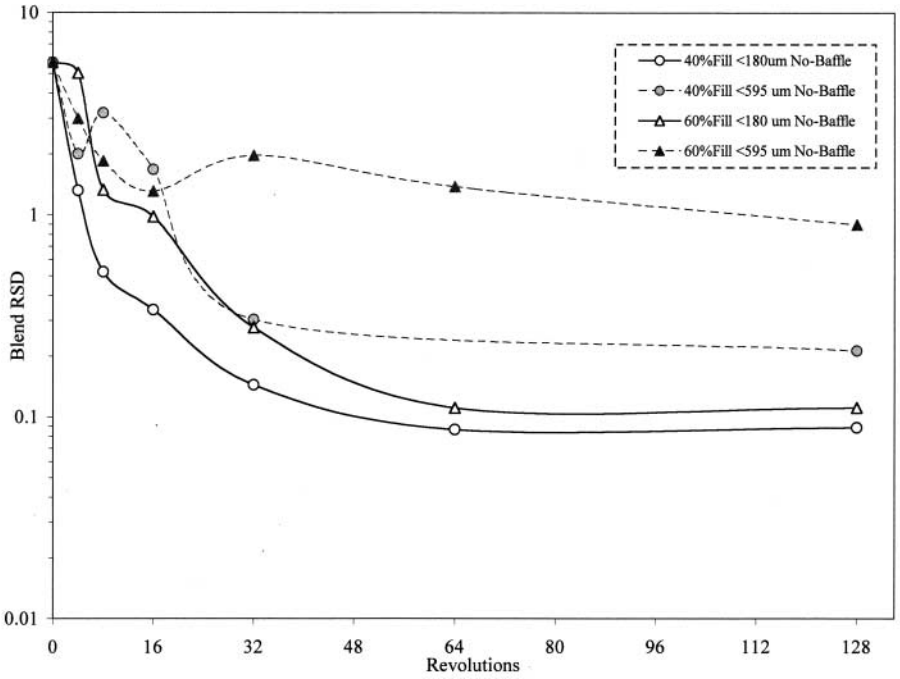

Figure 4. Comparison between the mixing curves of initially small and large NaCl (active) aggregates at 40% (circle) and 60% (triangle) fill levels without a baffle. Initially small aggregates (open symbols) were sieved below 180 μm, while the large ones (closed symbols) were sieved below 595 μm.

feasible alternative. Hill[26] found that pre-blending trace amounts of carbon black with polyethylene prior to dilution in a 250-cubic-foot double cone blender improved final homogeneity. Similarly, Samyn and Murthy[21] found that pre-blending milled aspirin with spray-dried lactose followed by dilution in a V blender equipped with an intensifier bar mixed the components faster and better than normal blending with or without an intensifier bar. Such a processing step has two advantages. First, the initial intensity of segregation is reduced since the active is pre-dispersed prior to final mixing. Second, the high shearing blades work to reduce the size of the agglomerates, thus aiding to develop a uniform texture for the mixture (bulk density and size). Figure 6a–c displays the mixing curves of the pre-blended and non-pre-blended cases for Formulation 1, Formulation 2, and Formulation 3, respectively.

It is apparent from Fig. 6a that pre-blending of the KCl at 3% concentration was not successful in appreciably reducing the RSD, possibly because the KCl agglomerates were initially very large in size (360 μm) and rigid. Once more, as in the normal blending operation, pre-blended material did not display a significant difference between the mixing rates of 40% fill and 60% fill, presumably because the inherent KCl particle size was not reduced. Doubling the dilution time to 240 revolutions for the 60% fill case verified that the mixing time was not the factor hindering further homogenization.

Similar to Fig. 6a, Fig. 6b indicates that pre-blending did not aid in improving the final homogeneity for pre-blended material with high KCl content (30%), Formulation 2. The mixing curves reached the same plateau and nearly collapsed at long time for the pre-blended and non-pre-blended mixtures, suggesting that initial active agglomerate size and strength were the limiting factors in improving the homogeneity.

The results of pre-blending Formulation 3, illustrated in Fig. 6c, were more encouraging. Figure 6c displays the RSD vs. the number of revolutions for three different NaCl mixtures at 40% and 60% fill capacities. The first mixture was sieved below 595 μm (initial mean aggregate size 360 μm), the second one was sieved below 180 μm (initial mean aggregate size 94 μm), and the third one was a pre-blended mixture of NaCl (94 μm) and microcrystalline cellulose. It is apparent that pre-blending the NaCl dramatically changed the outcome of the mixing

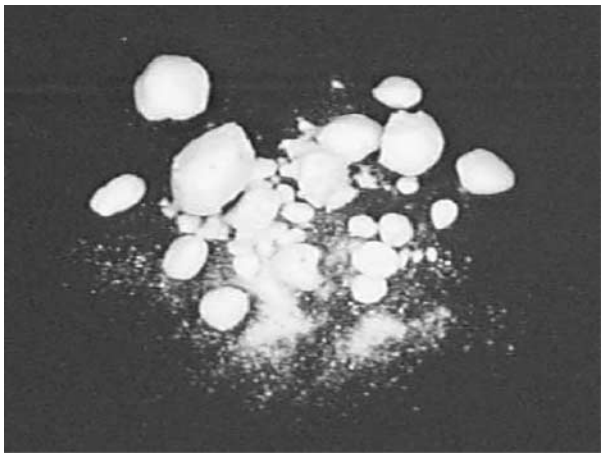

Figure 5. Photograph of active (NaCl) clumps sieved from the discharge of a 40% fill experiment after 32 revolutions. Hygroscopic materials such as salt can sequester moisture from surrounding components and agglomerate during blending.

step, producing a final mixture with an RSD value of nearly 2%, exceeding the usual acceptance criterion for blend homogeneity (5% RSD). As the aggregate size decreased, the rate of mixing and the final homogeneity improved. Contrary to the KCl used in Formulations 1 and 2, NaCl particles sieved below 180 μm had smaller initial aggregate sizes, and the shear imparted on the small quantity (3%) of NaCl was successful in enhancing the mixing process in two ways; it reduced the initial intensity of segregation, and it diminished the formation of agglomerates such as those shown in Fig. 5.

CONCLUSIONS

Previously developed experimental techniques for loading and sampling, along with a new method for sample quantification, were employed in this study to characterize mixing in a tote blender using a cohe-

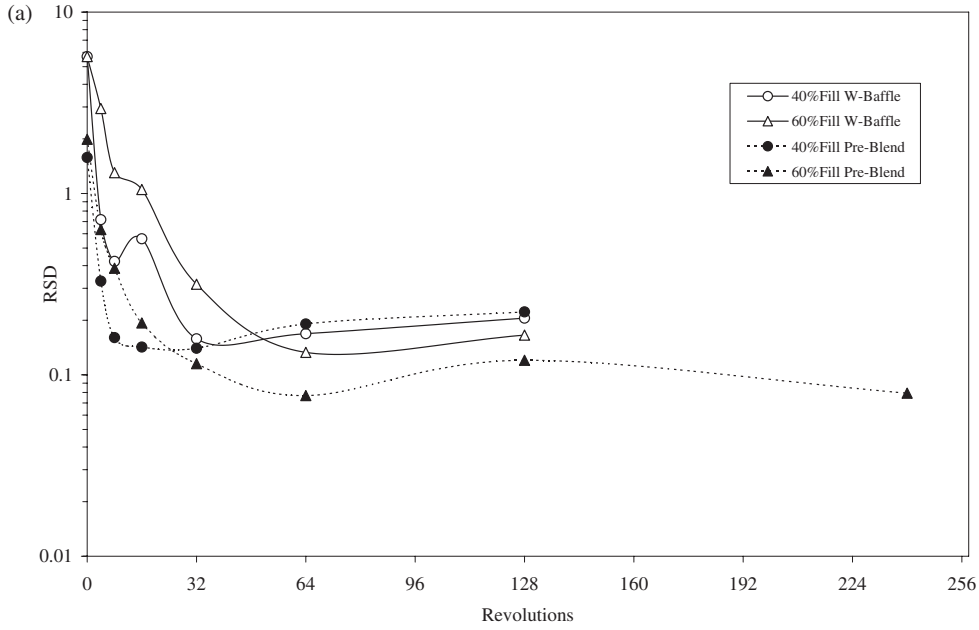

Figure 6. Effect of pre-blending on the mixing of Formulations 1, 2, and 3. Comparison between the mixing curves of pre-blended (closed symbols) and non-pre-blended (open symbols) formulations at 40% and 60% fill capacities. (a) The RSD plotted vs. the number of revolutions at 10 rpm for Formulation 1 (3% KCl). (b) The RSD plotted vs. the number of revolutions at 10 rpm for Formulation 2 (30% KCl). (c) The RSD plotted vs. the number of revolutions at 10 rpm for Formulation 3 (3% NaCl), illustrating the effects of changing the aggregate size on homogeneity.

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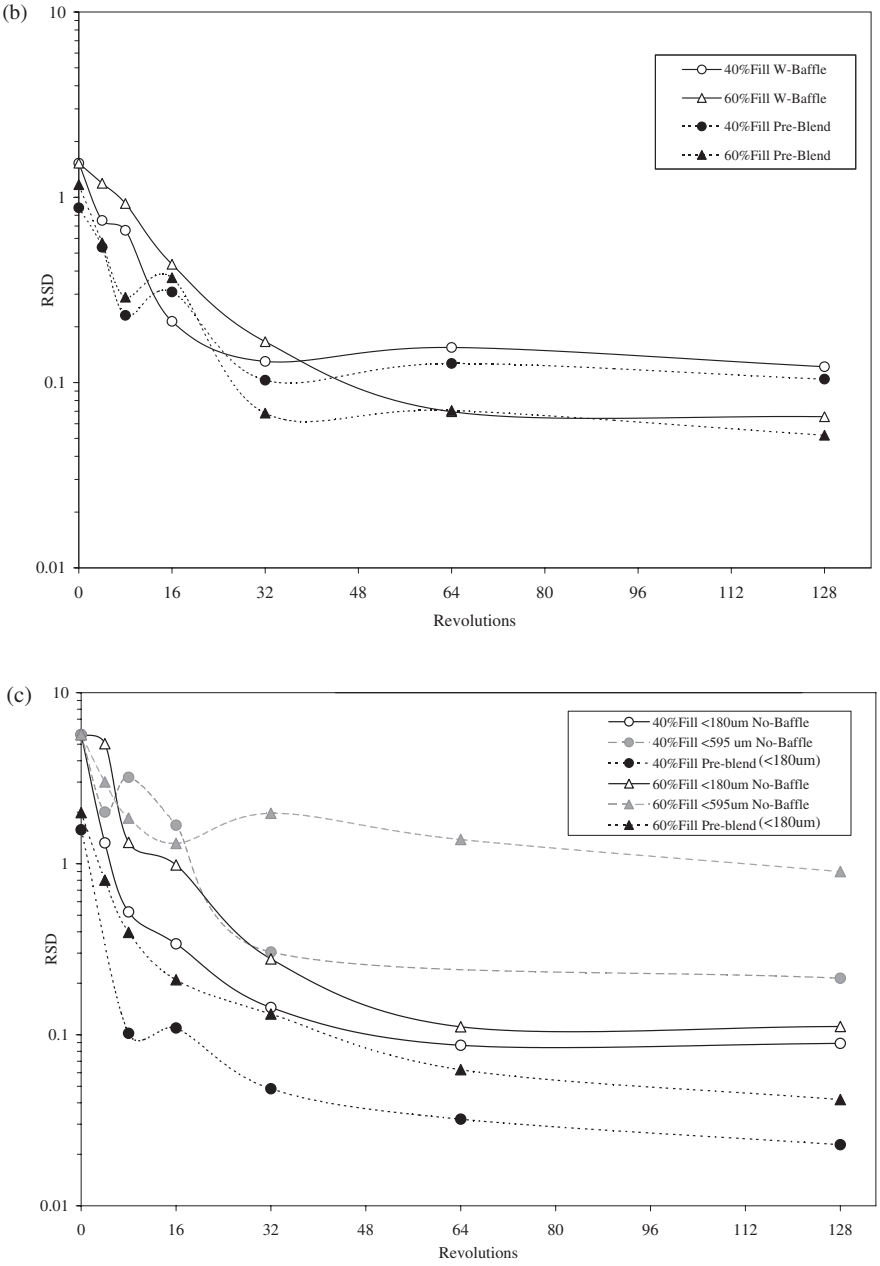

Figure 6. Continued.

sive placebo formulation. Process parameters such as fill level, mixing time, shearing, and baffle presence, along with material attributes such as initial active aggregate size and concentration, were varied to examine their roles in the degree of homogeneity of the final blend.

As shown in this article, active ingredients that have a tendency to agglomerate due to their strong cohesion, hygroscopicity, etc., can retard or even defeat the mixing process by forming clumps that prevent their dispersion throughout the bulk excipient. Such situations cannot be remedied with

standard internal baffles in tumbling blenders, since stationary baffles do not provide enough shear to break down aggregates.[21] An efficient and rather inexpensive step to overcome this problem is to introduce a high shear pre-blending step where the minor component gets pre-mixed with the excipient prior to dilution and coating. Provided that the initial agglomerate size and hardness of the material is not too large, as was the case in the NaCl formulation, high shear pre-blending can diminish the agglomeration process and prevent batch failure. For compounds that form large and rigid agglomerates, such as is the case with the KCl salt, pre-blending is ineffective. A pre-milling step where the material is crushed into smaller agglomerates followed by dilution into a blender equipped with an intensifier bar[21] might prove more effective.

Unlike the mixing of free-flowing materials, cohesive mixtures seem to be rather insensitive to mixing time since the mixing index (RSD) begins to plateau at a low number of revolutions (nearly 30). In addition, for agglomerating hygroscopic systems, there seems to be an optimum mixing time above which the degree of homogeneity deteriorates because more time is given for the hygroscopic material to sequester moisture and agglomerate. Similar to the free-flowing case, tumbling blenders perform poorly at high (80%) and low (20%) fill capacities due to low fraction material turnover per revolution. Experiments run at high fill levels lack free volume for the materials to turn over, while experiments runs at low fill levels experience sliding. Once more, 60% fill seems to be the optimal fill level for the tote blender for both free-flowing and cohesive systems.

Finally, the concentration of the active component did not affect the outcome of the mixing process; formulations at 3% and 30% KCl generated nearly identical results. The main factor influencing the success of the mixing batch for agglomerating systems was the cohesion of the active ingredient. The stronger the cohesive force, the more energy input is required to break up and disperse the large clumps that are formed, however, clumps might reform if a moisture-bearing excipient is added to the mixture. Clearly, mixing of cohesive hygroscopic material is primarily a "formulation" issue. Ingredient modification, leading to the control of agglomeration, is likely to be more fruitful than manipulating mixing equipment to achieve the desired final results.

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