INTRODUCTION TO STUDIES IN GRANULAR MIXING

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A common complaint of instructors in engineering and pharmaceutical science is the lack of laboratory experiments to teach powder processing. There are, for example, educational activities to demonstrate the effect of different variables in the particle segregation phenomena.[1, 2] Many of these activities, however, are not designed to test particles of industrial interest. It is even more rare that segregation measurements are part of a process development educational activity. Developing a pharmaceutical process, for example, involves understanding the impact of several process and material variables (*e.g.*, fill level of blender, speed of rotation, drug loading method) on the characteristics of a final blend (*e.g.*, homogeneity and segregation of minor components, flowability and density). In addition, the activity should also study the correlations among the various blend properties; for example, changes in flowability due to lubrication can hinder the dissolution of the drug. Pharmaceutical companies can benefit greatly from well-planned process development, especially when the activity can first be developed in the small scale.[3]

In this paper, a sequence of activities provides a concise yet illustrative training exercise to introduce students (and/or industry personnel) to some classic problems[4] in process development for granular solids. We focus on a pharmaceutical example where the mixing operation is expected to yield a blend with specific drug and lubricant homogeneity. Events

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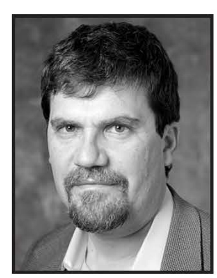


such as segregation and agglomeration of the minor components, which can adversely affect homogeneity, are examined. Techniques to measure both homogeneity and segregation tendencies are discussed. The density and the flowability of raw materials, drug preblends, and lubricated blends are measured and correlated. The activities are designed for a class of typically 20 students, which allows separating them into groups that will later compare and discuss the effect of using different operating conditions.

In the Materials and Methods section, the techniques needed to measure each of the properties of interest are described. The Results section presents and discusses the measurement obtained by a group of students. A Summary and Conclusion section provides concluding remarks.

MATERIALS AND METHODS

Raw materials

The formulation contains the following components: 84% Fast Flo lactose (Foremost Farms), 15% acetaminophen (APAP, Mallinckrodt) and 1% magnesium stearate (Mallinckrodt). The mass of each component to be added to the blender is given by the different terms on the right side of Eq. (1).

$$\text{Volume} = \frac{w}{\rho_{Ace}}.15 + \frac{w}{\rho_{Lac}}.84 + \frac{w}{\rho_{Mg}}.01 \qquad (1)$$

where ρ_{Ace}, ρ_{Lac}, and ρ_{Mg} are the bulk densities of acetaminophen, lactose, and lubricant respectively, and w is the total mass of all materials. The bulk density of materials is measured following the procedure described in the section "Testing bulk and tapped density.".

Activities

The process (Figure 1) entails preblending drug (APAP) and excipient (*i.e.*, lactose) and, in a second mixing step, adding the lubricant (magnesium stearate) to the formulation. Properties are measured for the raw materials, for the drug pre-blend, and for the lubricated blend. Different groups of students (if possible) should use different conditions for the blender, such as fill level (40% of the total volume, 80%, etc.) and initial layout of the minor component in the blender (layered, one side, etc). The details to perform blending and measure each blend parameters are given in subsequent sections.

Blending APAP and lubricant (in a V-blender or other tumbling blender)

The blender is used in two steps, first to prepare a pre-blend of APAP and excipients, and second to mix the lubricant with the pre-blend. Having several groups of students gives the possibility to study the impact of blender parameters.[5] In the present case, two teams operate the 1 cu. ft V-blender at 40% of its total capacity (*i.e.*, 0.4 cu. ft.), loading the APAP either through a single side or with a layered method (Figure 2). In the side method, all the lactose is loaded first into the blender, then all the APAP is introduced into one of the shells of the V-blender (Figure 1). In the layered method, half of the lactose is added into the blender, then all the APAP is evenly distributed in a layer, and finally, the rest of the lactose is added on top of the APAP (Figure 2). The other two teams operate the blender at 80% capacity (0.8 cu. ft), using the same two loading methods for the APAP. Once the V-blender is loaded, it is operated at 30 rpm for 10 minutes. After mixing, two groups of five samples each are collected from each shell of the blender using a Globe-Pharma thief (New Brunswick, NJ) or similar. A thief is an instrument to extract samples from a powder bed. Each sample is collected at a different depth of the shell (Figure 3) and transferred to a glass vial to determine chemical composition using a suitable analytical method. Additionally, a 300-gram sample is extracted to perform density, flowability, and segregation measurements.

Next, the magnesium stearate (lubricant) is added into the blender through the valve at the bottom (Figure 1) and mixed for another 10 minutes at 30 RPM. Samples are collected again from both shells with the Globe-Pharma thief and a 200-gram sample of the blend is taken to measure density, flowability, and the segregation of APAP and magnesium stearate. The composition of these samples is determined with a suitable analytical method.

Sampling the blender (Global Pharma thief or other)

Sampling is the most important task for assessing homogeneity. The FDA provides guidance regarding tools and methodologies,[6] and more importantly, most sampling tools have been characterized.[7,8] The thief sampler (Global Pharma) is one of several sampling tools available. The thief is inserted into the blend, and the operator opens the sampling cavities using a handle at the other end of the sampler. Powder fills the cavities, which are subsequently closed, trapping the powder samples. The design of the thief allows extracting one to three samples at a time. Samples are 0.5-1.5 grams each, depending on the size of removable dies used.

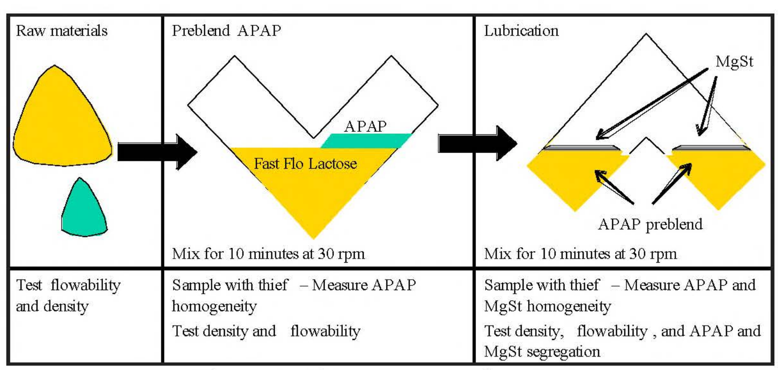


Figure 1. *Three stages in the mixing process development.*

Determine sample concentration (NIR or other technique) and homogeneity

There are many techniques available to determine APAP and lubricant concentration in samples (*e.g.*, UV, titration, conductimetry, NIR). Although USP recommends a technique for a given component, sometimes there are situations in which it is necessary to consider alternative analytical methods. For an educational activity, the instrumentation available in the lab may determine the selection of the technique. The technique used in the present study is NIR spectroscopy, a non-destructive technique[9, 10] that allows a fast assessment of concentration because it does not require sample dissolution (as in UV or conductimetry) or any other sample preparation (although it assumes that the sample itself is homogeneous). The technique requires developing a calibration equation using standard samples with a known drug concentration. Chemometric software (application of mathematical or statistical methods to chemical data), typically provided by the NIR instrument, facilitates the selection of the most appropriate standards to build the calibration equation based on the spectra collected and on the concentration of each standard.

The sample concentrations are used to estimate one of the many indexes available to determine the homogeneity of minor components (APAP and MgSt) in the blend. The index most commonly used in industry is RSD (relative standard deviation).

$$RSD = \frac{s}{\bar{C}} \quad (2) \qquad \text{where } s = \sqrt{\frac{n\sum_{i=1}^{n} C_i^2 - \left(\sum_{i=1}^{n} C_i\right)^2}{n(n-1)}} \quad (3)$$

In the previous equations, s is the standard deviation of all sample concentrations, $\bar{C}$ is the average concentration, C_i is the concentration of each individual sample, and n is the total number of samples. The more homogeneous the mixture, the smaller the RSD index. In general, an acceptable value would be below 5% based on samples of ~0.5 grams that are completely assayed by the analytical method.

Measuring segregation (Sifting Segregation Tester)

Segregation of components is one of the main reasons for heterogeneity of pharmaceutical formulations. The segregation tester used here (Jenike & Johanson, Tyngsboro, MA) determines sifting segregation, one of the most common types of segregation for pharmaceutical materials.[11, 12] When the flowing layer dilates (a powder usually expands when flowing), smaller particles percolate through a matrix of larger ones. The sifting mechanism is most likely to occur for particles of different size when they flow during filling, transfer, etc.

The tester consists of a steep angle and a shallow angle cone (hoppers), with the steep one initially placed above the shallow one. The upper hopper is filled with the formulation, which is discharged into the lower hopper and then recirculated into the upper hopper. This process is repeated 10 times in order to maximize segregation. Finally, several samples are collected at the discharge of the lower hopper and their concentration determined with NIR.

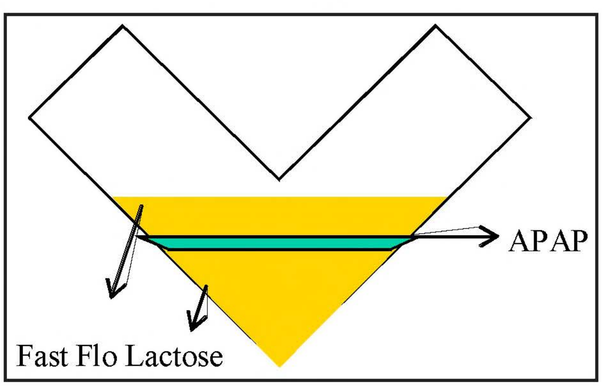
Testing bulk and tapped density

The bulk and tapped densities are evaluated for the raw materials, for the APAP blend, and for the lubricated blend. The compaction ability of a powder or blend is an important property because it correlates with its ability to flow. Additionally, it can be used to estimate the amount of material that will go into the dies of a tableting machine.

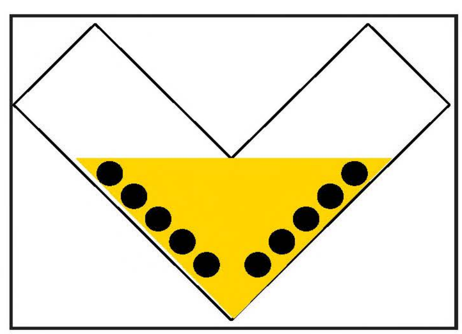
Bulk density is evaluated by filling a 100 ml graduated cylinder with material and determining its net weight. In order to determine the tapped density, the cylinder is "tapped" ~1000 times in a density tester (VanKel, Model 50-1200) and the new volume for the same amount of material is measured. The tester provides a fixed drop of one-half inch at 300 taps/min.

Measuring flowability (prediction and flow tester)

Flowability should be assessed for the raw materials, for the preblend of APAP, and for the lubricated blends. The flowability of powders and blends can be assessed using predictive correlations and direct experimental measurements. Among the predictive correlations, there is the Carr index,[13] which uses the bulk and tapped density to estimate the flowability of the blend. Flowability is classified according to the value of the Carr compressibility index (C.I. = (tapped density – bulk density)/tapped density * 100) as: Excellent (0-11%), good (12-16%), fair (18-21%), poor (25-35%), and very poor (>33%).



◄ ***Figure 2.*** *V-blender loaded with the layering method.*



► ***Figure 3.*** *Sampling positions.*

The flowability of blends can be measured using a number of devices (*e.g.*, hoppers, flow testers). In the activities reported here, flowability is measured using a flow tester (PTG-S3 system). This instrument measures the time it takes for 100 grams of material in a funnel to flow through a specified pouring nozzle. When powder flow starts, it is detected by two IR sensors, which activate a timer. As soon as there is no more powder flow, the funnel is closed and the timer stops. A stirrer is sometimes needed in the funnel as some pharmaceutical materials will not start flowing without assistance. The test should be repeated five times, and the deviation of results should not exceed 5%.

The comparison of flow indexes and the direct flow measurements is an interesting exercise that allows students to understand the correlation between ability to densify and flowability.

TYPICAL RESULTS

Bulk and tapped density, and flowability of pure materials and blends

The density measurements are used to estimate the amount of material needed to load the blender, and to estimate the Carr compactability index (an indication of the compressibility of a powder). Bulk and tapped density measurements are performed four times (each group takes one measurement) using the 100 ml graduated cylinder, and the average and standard deviation are calculated. Table 1 shows the average and the standard deviation of the four values. As expected, bulk densities are always lower than tapped densities, and lubricated blends are more dense than the premix. In general, there is more uncertainty (larger standard deviation) in the measurement of bulk density because it is more sensitive to the manner of loading the graduated cylinder (*i.e.*, effect of the operator). In the case of lubricated blends, the different conditions of operation (*i.e.*, fill level and loading of minor components) of the blender introduce an additional source of variation for the measurement.

The flowability of raw material and blends is predicted with the Carr index and measured using the Flow tester PTG-S3 (Table 2). Preblends of APAP do not flow through the tester. Lubricant addition improves the flowability in all cases.

Homogeneity and segregation of minor components

Table 3 shows the APAP concentration of samples extracted from the right and left shell (R or L) of the V-blender in the APAP preblend step and in the lubrication step. In the same table, the average concentration, the standard deviation of concentration [Eq. (3)] and the homogeneity index [Eq. (2)] are estimated for each shell of the blender and for the entire blender for

TABLE 1
Bulk density (B.D.) and tapped density (T.D.) for different materials (gr./ml) and the standard deviation of the measurements (of 4 readings).

Raw materials	APAP preblend	Lubricated Blend
Lactose. B.D.: 0.613 (2.26 %), T.D.: 0.695 (3.62 %) APAP. B.D.: 0.355 (3.75 %), T.D.: 0.588 (1.67 %)	B.D.: 0.529 (3.89 %), T.D.: 0.690 (1.19 %)	B.D.: 0.645 (2.02 %) T.D.: 0.798 (1.23 %)

TABLE 2
Flowability Indexes (C.I.) and Measurements (PTG-S3)

Raw materials	APAP preblend	Lubricated blend
Lactose. C.I.: 11.8; PTG-S3: 5, 5.3, 5.7, 5.7 sec. APAP. C.I.: 39.67; PTG-S3: no flow	C.I.: 23.24; PTG-S3: no flow	C.I.: 19.20; PTG-S3: 8.9, 12.1, 11.1, 10.3 sec.

TABLE 3
APAP Concentration Values for the Right (R) and Left (L) Legs of the Blender

	APAP in preblend				APAP in lubricated blend			
	series 1		series 2		series 3		series 4	
conditions	80%, top-bot	40%, top-bot	80%, side-side	40%, side-side	80%, top-bot	40%, top-bot	80%, side-side	40%, side-side
R1	13.61	12.94	12.30	10.31	14.88	14.62	14.39	15.62
R2	13.53	13.61	12.55	10.12	14.54	14.81	14.09	14.47
R3	13.02	14.77	21.85	11.34	14.87	14.92	14.76	15.05
R4	13.62	13.47	12.81	11.93	15.69	14.76	15.81	15.20
R5	13.27	13.93	12.94	13.06	15.64	14.64	17.61	14.96
R - Average	13.41	13.74	14.49	11.35	15.12	14.75	15.33	15.06
R - SD	0.26	0.68	4.12	1.21	0.51	0.12	1.43	0.42
R - RSD %	1.92	4.92	28.46	10.63	3.40	0.84	9.32	2.77
L1	13.16	13.07	12.50	12.64	15.46	15.11	15.53	17.44
L2	12.77	14.51	12.81	12.95	14.73	14.87	14.78	14.90
L3	19.90	13.01	12.32	12.95	15.28	14.91	14.32	15.47
L4	13.83	15.56	13.46	12.68	15.47	15.36	15.82	14.49
L5	13.64	12.76	12.87	14.77	16.05	14.88	16.04	17.14
L - Average	14.7	13.8	12.8	13.2	15.40	15.02	15.30	15.89
L - SD	3.0	1.2	0.4	0.9	0.47	0.21	0.72	1.33
L - RSD %	20.2	8.8	3.4	6.7	3.07	1.39	4.74	8.37
Total Average	**14.0**	**13.8**	**13.6**	**12.3**	**15.26**	**14.89**	**15.32**	**15.47**
SD	**2.1**	**0.9**	**2.9**	**1.4**	**0.49**	**0.22**	**1.07**	**1.03**
RSD %	**14.9**	**6.7**	**21.3**	**11.4**	**3.20**	**1.46**	**6.98**	**6.63**

different APAP loading conditions and fill levels. In Figure 4, the global RSD values for APAP are plotted as a function of fill level of the blender. Four series of data can be identified in this figure; the first two correspond to the RSD for APAP in the preblend (one series for each APAP loading method) and the last two correspond to the RSD for APAP, after lubricating the preblends. The top-bottom loading method for APAP always leads to more homogeneous blends (smaller RSD values) than the side-side loading method (series 1 has larger values than series 2 and series 3 has larger values than series 4). Lubrication enhances APAP homogeneity (series 3 has smaller RSD values than series 1 and series 4 has smaller values than series 2). A larger fill level always leads to a less homogeneous mixture (*i.e.*, larger RSD value), and this variable has a larger impact at short mixing times (series 1 and 2) than at longer mixing times (series 3 and 4). These variables do not have an effect on the homogeneity of the different shells.

The APAP and lubricant segregation tendencies are determined using portions of the lubricated blend. The blend portions are processed with the segregation tester, and the segregation index is estimated using a group of samples collected at the outlet of this tester. Table 4 compares the RSD of the initial blend and the RSD of the samples from the segregation tester for APAP and for the lubricant. The RSD of APAP in the blender is larger than the RSD index of the segregation samples. Not only does the blend not segregate, but, in fact, more mixing occurs as we pass the blend through the funnels of the segregation tester, yielding more homogeneous samples. Therefore the RSD in the blender is not affected by APAP segregation, and instead reflects the effects of fill level and loading method.

Conversely, the RSD index for magnesium stearate in the blender is, in general, smaller than for the segregation samples (Table 4). This indicates that the homogeneity of magnesium stearate becomes worse in the tester as a result of segregation.

Summary: Main observations

The activities show that the APAP homogeneity is affected by the loading method of APAP, the fill level of the blender, and the lubrication of the blend. The segregation test shows that while the APAP does not segregate, the lubricant does. Lubrication leads to the densification and the improved flowability of the blends. In order to carry out the homogeneity test in a reasonable time frame, the sampling of the blend is not extensive (~10 samples). Although this does not confer a strong statistical significance to the homogeneity results, the results obtained by different groups are coherent and show trends and effects of different variables (*e.g.*, fill level and method of loading for homogeneity).

CONCLUSIONS

The main objective of this paper is to present an activity illustrating several aspects of pharmaceutical powder process development. The procedure to evaluate blend properties (homogeneity, segregation, density, and flowability) is described and the analysis of results takes inter-relations among properties of the blend (*e.g.*, between segregation and homogeneity, between flowability and density) into consideration. If several groups of students are available, then there is the possibility to study the effect of operating parameters of the blender (*e.g.*, fill level, loading method of minor components) on blend properties.

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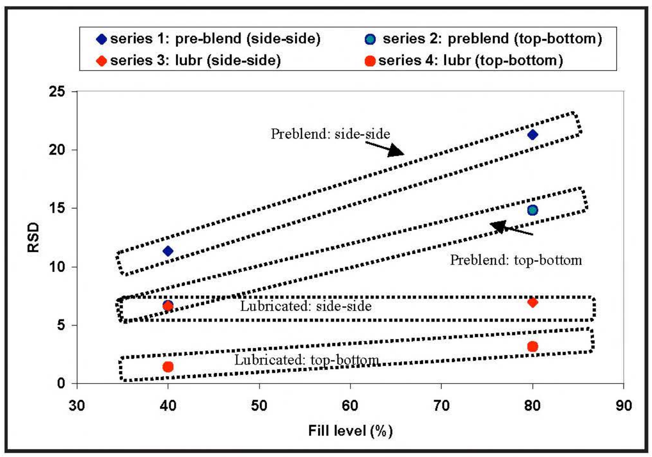

Figure 4. *Effect of fill level, loading method and lubrication on the APAP RSD.*

TABLE 4

Comparison of Homogeneity in the Blender and Segregation indexes for APAP and MgSt

	APAP				Lubricant			
capacity (%)	80	40	80	40	80	40	80	40
loading method	top-bot	top-bot	side/side	side/side	top-bot	top-bot	side/side	side/side
Blender	14.86	6.70	21.30	11.36	4.03	6.57	10.01	4.35
Segregation test	3.61	7.46	5.33	3.54	9.02	17.49	9.19	9.06

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