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A Homogeneity Study Using NIR Spectroscopy: Tracking Magnesium Stearate in Bohle Bin-Blender

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ABSTRACT

A method was developed for studying mixing of cohesive pharmaceutical mixtures. A combination of accurate sampling and NIR spectroscopic analysis was developed as a suitable method to determine homogenization of magnesium stearate as a function of blending variables. A typical pharmaceutical blend containing a ratio 35:64:1 lactose, avicel, and magnesium stearate was used as a model system. The method accounted for variability of the concentration of magnesium stearate as well as variability of the excipients. Levels of magnesium stearate as low as 0.05% could be resolved by the method, and showed a predicting confidence interval above 98%.

Key Words: Near-infrared; Infrared; NIR spectroscopy; Magnesium stearate; Powder blending; Homogeneity; Lubrication; Pharmaceutical blends.

1. INTRODUCTION

Powder blending is governed by three major mechanisms: convection, dispersion, and shear.[5] The dominant mixing mechanism, and consequently the overall performance of the blender, depends greatly upon the physical properties of the mixing materials, the type and geometry of the blender as well as the operating conditions. The homogeneity of a pharmaceutical blend is usually determined by assessing the uniformity of the active ingredient distribution throughout the mixture while the uniformity of the excipients is assumed. Blending of powder is often addressed with analytical techniques

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used to track the active component in the mixture. While the sampling method is unquestionably a very important aspect of assessing the blend homogeneity, very few studies focus on the sampling techniques that characterize mixing behavior of powder for the target blender. Moreover, there is a growing consensus that available sampling techniques are grossly inadequate for the intended task. For recent reviews on sampling techniques, see Alonso and Alguacil[1] and Muzzio et al.[8]

Inefficient blending has two major causes: (i) poor equipment design, and (ii) particle segregation (driven by differences in particle properties). In addition to inefficient blending, addition of a lubricant to pharmaceutical formulations (a common practice in most tableting processes) can impart undesirable characteristics to tablets. Typically used lubricants in pharmaceutical applications are magnesium (Mg) stearate, stearic acid, and paraffin. They allow compression at lower pressure and, hence, reduce the generation of heat during tablet compression. This effect depends upon the amount and intensity of shear energy applied to the lubricated mixture. The interactions between the lubricant and excipient(s) or between the lubricant and the active ingredient could cause slow dissolution and insufficient mechanical strength of tablets and capsules. Poor lubrication may lead to variability in the compaction step (e.g., the tablet will stick to the press) and may hinder flowability. Over-lubrication occurring when lubricants completely coat the particles surface should also be avoided. When a mixture is over-lubricated, the binding between particles and the strength of the tablets decrease, resulting in an increase of the disintegration and dissolution time.[6,7,9,10] Consequently, the amount of lubricant should be chosen to provide optimal compression properties without compromising dissolution of the drug or the tablet's mechanical strength.

Mg stearate is used in capsule and tablet-making processes to facilitate the flow of the drug into the tableting and encapsulating machinery. In order to develop protocols that minimize the two-limit problem of under- and over-lubrication, it is desirable to monitor Mg stearate during a blending process. In this article, the mixing characteristics of a mimic pharmaceutical blend are addressed by quantifying Mg stearate distribution in a Bohle bin-blender. The mixture consists of avicel, lactose, and Mg stearate with the corresponding ratios 35:64:1 by weight. We use the core sampling technique that was developed by Muzzio et al. and diffuse reflectance NIR spectroscopy to detect Mg stearate.

2. MATERIAL AND METHODS

2.1. Material and Equipment

The materials used were avicel PH101 (microcrystalline cellulose), lactose (lactose monohydrate N. F.), and Mg stearate provided by Merck & Co®. Particle size distribution of these materials was obtained using a Laser Scattering Particle Size Instrument (Microtrac). This scattering technique is valid for determining particles in the size range from 0.7–75 microns. Particle size data for lactose, avicel, and Mg stearate are presented in Fig. 1a–c.

The blender was manufactured and assembled at Rutgers University. The sampling cores, Fig. 2, were steel tubes of an outer diameter $\frac{3}{4}$ inch and an inner diameter $\frac{11}{16}$ inch. The length of the tubes spanned the height of the blender for ease in extracting samples. The sampling vials were 20 mL disposable scintillation glass vials (Fisher Scientific®).

The Rapid Content Analyzer (model 6500) is manufactured by FOSS NIRSystems, Inc®. The instrument consists of a monochromator unit and a detector unit that are controlled by an external PC. The software, Vision (version 2.51), collects the sample spectra and can apply various mathematical treatments and statistical methods to the data.

2.2. Methods

2.2.1. Sampling Preparation

The sample size was kept constant at approximately one (1.0) gram or 10 mm. This size of the sample was chosen so that the sample thickness stayed within the effective range for NIR spectroscopy reflectance mode. That is, the depth of the sample is sufficient so that all Mg stearate presence in the sample is detected, and no radiation escapes the other side. Approximately 5 to 35 samples were obtained per sampling core depending upon the vessel fill level and the location of the core. A total of 13 cores was used in the study, resulting in approximately 100–300 samples per experiment. Figure 2 shows the sampling core as well as the sampling locations in the Bohle tote-blender. The sampling locations were chosen to obtain the maximum number of samples that were representative throughout the blender. In order to minimize perturbations to the powder bed during sampling, all cores were inserted before any of them were removed.

2.2.2. Near-Infrared Spectroscopy

A set of 31 samples of known concentration that span the working concentration range and are representative of the manufacturing variability was assembled. In this study, the reference samples were selected according to the concentration of lubricant, Mg stearate. The minimum value was 0.0% and the maximum was 3.0% with increments of 0.1%. The ratios of lactose to avicel in these samples were premixed and randomized in 35:65 proportions according to Eq. (1), in which $C_{\text{desired avicel}}$ is 65%; and ε is a randomized vector of values between $(-1, +1)$. This equation gives a span of randomized avicel concentration from 45 to 85%, which accounts for the variations of avicel and lactose concentrations

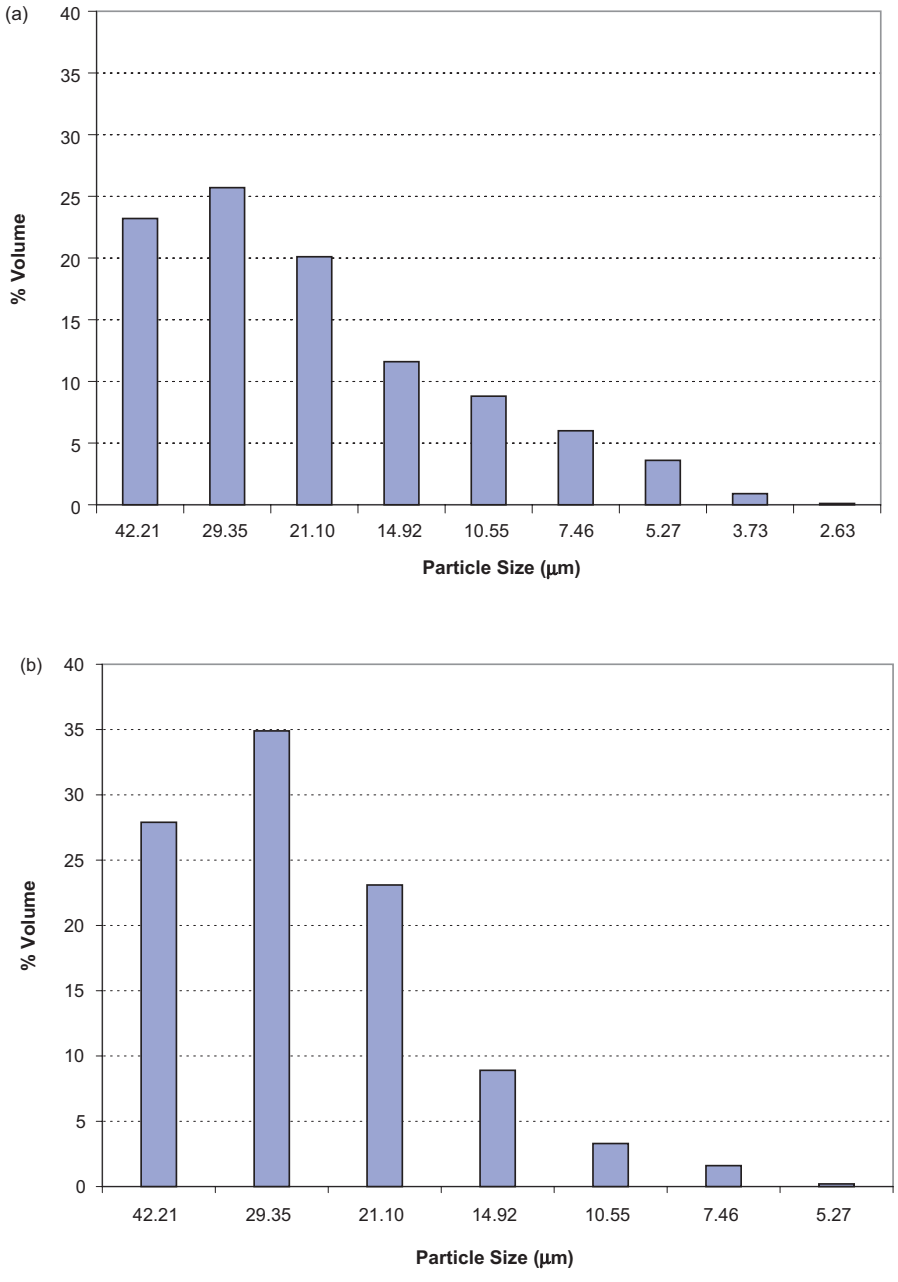

Figure 1. (a) Particle size distribution—avicel. (b) Particle size distribution—lactose. (c) Particle size distribution—magnesium stearate.

(*continued*)

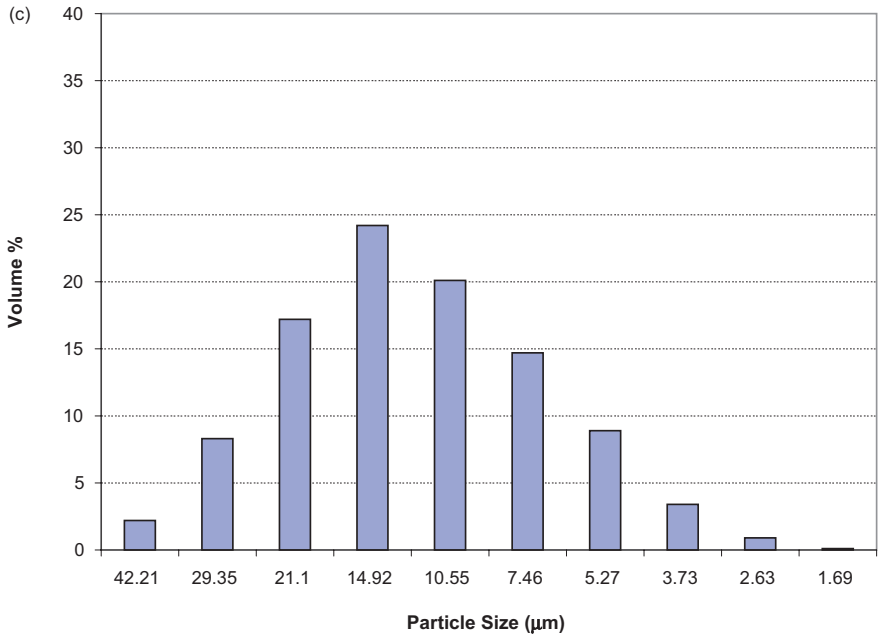

Figure 1. Continued.

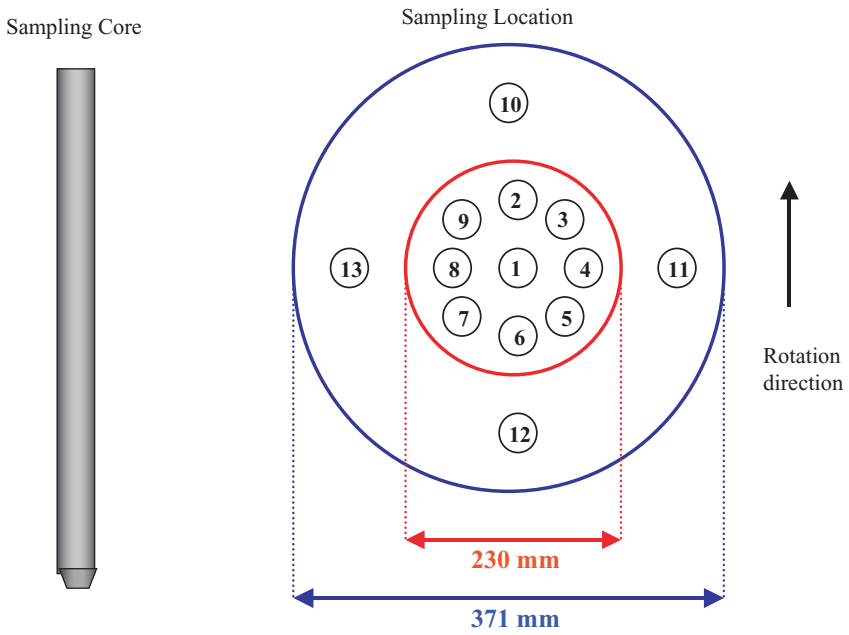

Figure 2. 40L Bohle-tote blender—sampling core and sampling location.

due to imperfect blending of excipients during the actual experiments.

$$C_{\text{target avicel}} = C_{\text{desired avicel}} + 0.3^{*}C_{\text{desired avicel}}{}^{*}\varepsilon \quad (1)$$

The reference samples were prepared at 10 grams each. One out of 10 grams was weighted and used for the NIR spectroscopy reference set. Quantitative analysis method was used to determine Mg stearate concentration. The partial least square (PLS) method with

the second derivative treatment was applied to the collected spectra of the reference samples. The second derivative treatment was selected to eliminate spectral offset and slope variation within a set of spectra that are caused either by changes in the instrument response or particle size differences among the samples. The segment size used for the second derivative is 20 while the gap is zero. These values, recommended by the manual, are suitable for most applications. The PLS regression was performed on the entire spectra region (1140–1830 nm) with leave-one-out cross validation. This accounts for both the variability of Mg stearate concentration and the variability of lactose to avicel ratios in the samples. A USP standard procedure of validation was used to examine the accuracy, precision, ruggedness, and robustness of the model. Once the model was validated, it was used to predict the Mg stearate concentration in the samples from the blending experiments.

2.2.3. Blending Experiments

The Bohle bin-blender was loaded with the materials arranged in horizontal layers (top-to-bottom loading fashion). This loading method was selected because it is known that radial dispersion in tote blenders is slower than axial convection.[8] Lactose and avicel were premixed before the addition of magnesium stearate. The following matrix of experiments was carried out:

- Vessel filling level: 85% of the total vessel volume.
- Speed: 14 rpm.
- Blending time: 10, 20, 40, 80, and 160 revolutions (independent experiments started from identical initial conditions).

3. RESULTS AND DISCUSSION

3.1. NIR Spectroscopy

Table 1 shows the composition of the samples from the reference set. The multiple correlation coefficient (or coefficient of multiple determination), R^2, with the chosen PRESS factor five, is 98.11%. The PRESS factor or Prediction Residual Error—Sum of Squares was calculated by Vision. (For additional information on the details of the PRESS factor, readers could refer to Vision manual.) This PRESS value included an optimal balance between the robustness of the model and R^2 value. This choice of five factors gave a roughly uniform distribution of predictive error over the calibration range (0.0–3.0%) and avoided extreme deviation at the high end of the intervals which were observed when fewer factors were used. Figure 3 shows a plot of PRESS factors generated by the model. Both calibration set and validation set, with the chosen PRESS factor, show very good agreement between calculated and prepared samples of known Mg stearate concentration (lab data) samples under the desired range.

Table 1. Composition of the calibration set.

Sample numbers	Mg stearate (%)	Avicel (%)	Lactose (%)
1	0.00	56	44
2	0.10	71	29
3	0.20	79	21
4	0.30	61	39
5	0.40	60	40
6	0.50	60	40
7	0.60	57	43
8	0.70	51	49
9	0.80	55	45
10	0.90	57	43
11	1.00	75	25
12	1.10	54	46
13	1.20	61	39
14	1.30	79	21
15	1.40	78	22
16	1.50	53	47
17	1.60	77	23
18	1.70	55	45
19	1.80	72	28
20	1.90	60	40
21	2.00	78	22
22	2.10	63	37
23	2.20	61	39
24	2.30	76	24
25	2.40	68	32
26	2.50	77	23
27	2.60	71	29
28	2.70	58	42
29	2.80	68	32
30	2.90	73	27
31	3.00	74	26

3.2. Blending Experiments

Homogeneity of a blending mixture is assessed by plotting the mixing curve (or relative standard

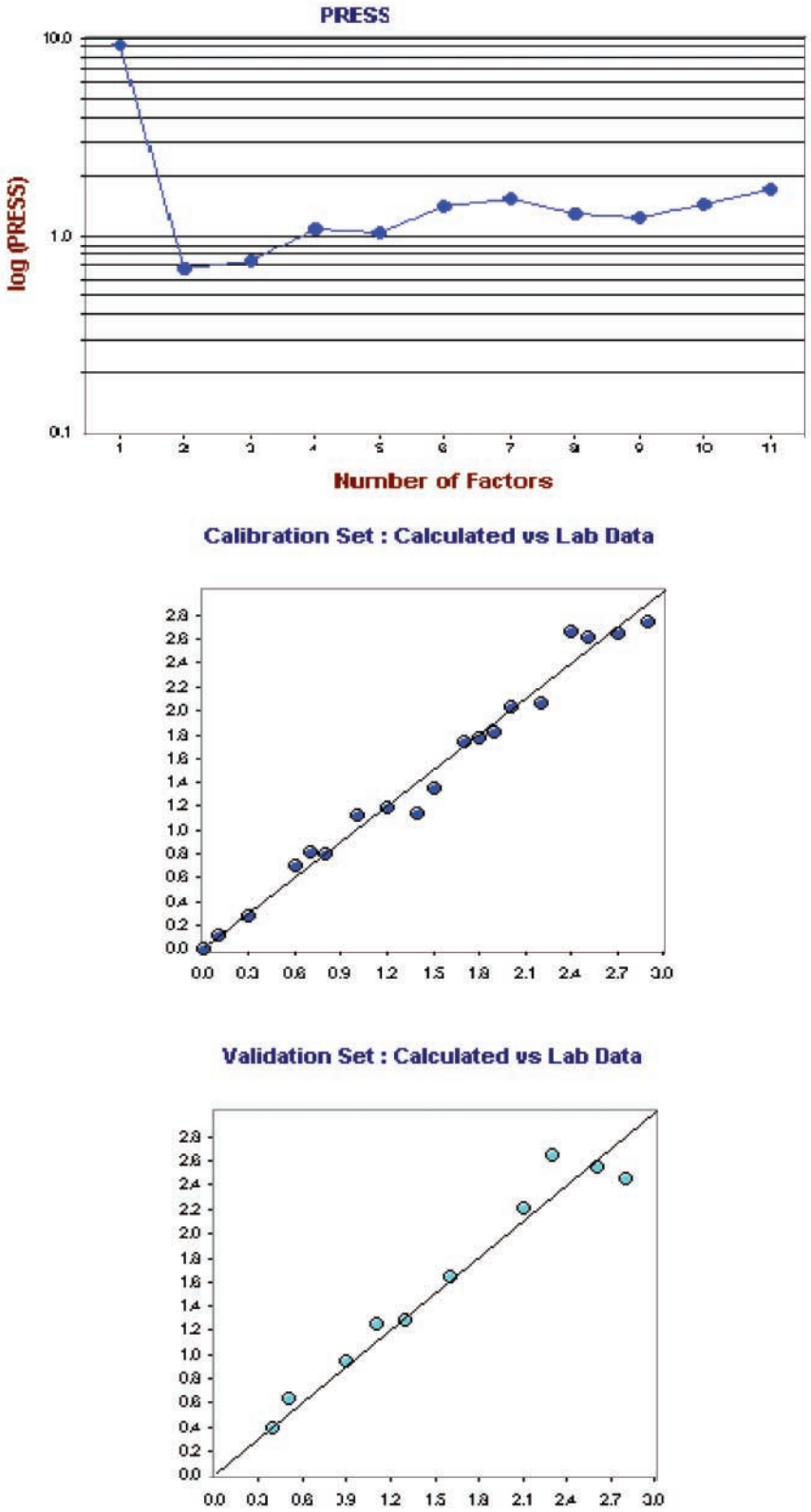

Figure 3. PRESS factor, calibration, and validation sets.

deviation vs. mixing time). This method has been discussed in detail by Muzzio et al.[8]. The mixing curve, Fig. 4, was obtained under the conditions listed in Sec. 2.2.2. The relative standard deviation was calculated using Eqs. (2) and (3) where N is the total number of samples in one experiment, $\overline{C}$ is the theoretical average concentration (1.0%), and C_i is the sample concentration measured using the NIR spectroscopy. Typical behavior of mixing curves for cohesive materials shows a decay in RSD values at short mixing time and a slow transition to an asymptotic RSD value at longer mixing time. For convective mixing processes characteristic of top-to-bottom loading patterns, the asymptotic regime is usually approached after approximately 50 mixer revolutions, and is independent of mixer speed, blender type, and the degree of cohesivity of the powders.[2,11]

$$\mathrm{RSD} = \frac{\sigma}{\overline{C}} \tag{2}$$

$$\sigma = \sqrt{\frac{\sum_{i=1}^{N} (\overline{C} - C_i)^2}{N-1}} \tag{3}$$

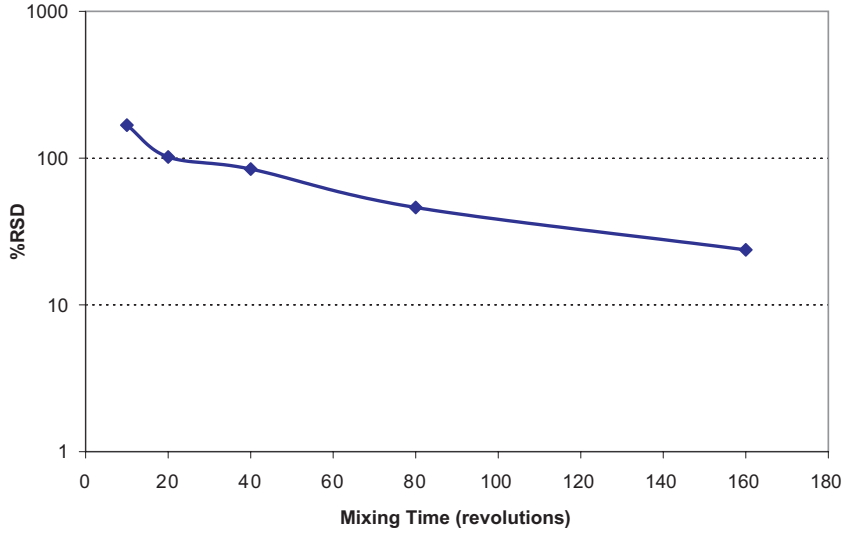

Figure 4. Mixing curve at 85% fill level—14 rpm—no baffles.

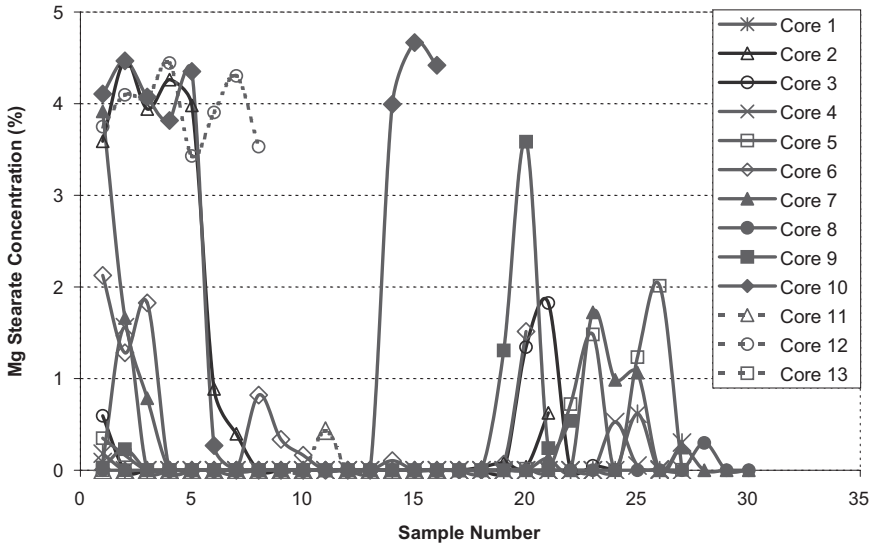

Figure 5a. Concentration profiles at 85% fill level—14 rpm 10 revolutions—no baffles.

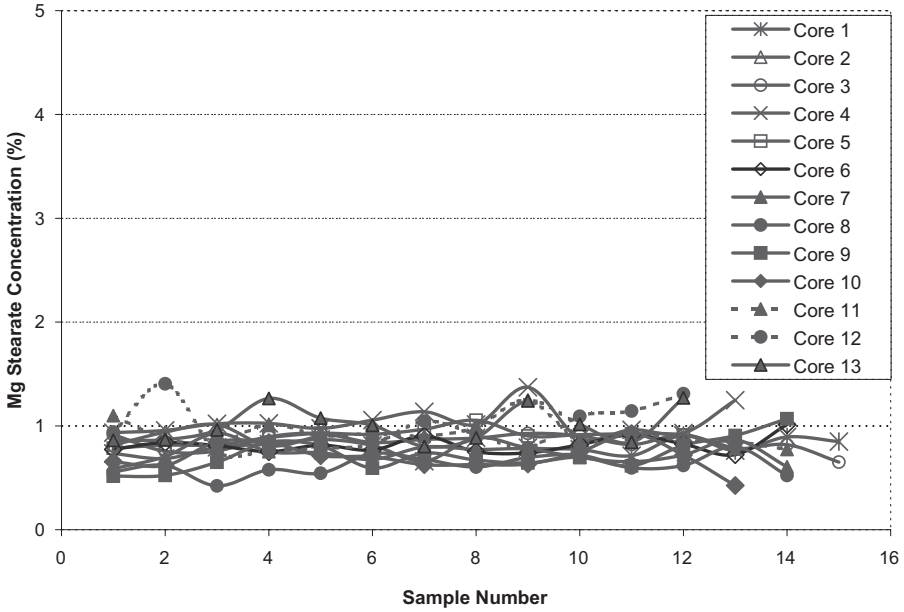

Figure 5b. Concentration profiles at 85% fill level—14 rpm 60 revolutions—no baffles.

Figure 5a showed Mg stearate concentration found in each core for the 85% vessel fill level case after one minute of blending. Mg stearate concentration was high in the first and last few samples of cores 1, 2, 10, and 12, but not in the middle samples of the cores. This confirms that most Mg stearate, at this short mixing time, stayed either on the top or the bottom of the powder bed due to its initial loading. Mg stearate did not have enough time to travel elsewhere in the blender, resulting in zero concentration in the middle of these cores. Since the blender rotation direction was from core 12 to 10 (see Fig. 2), cores 2, 10, and 12 had the most Mg stearate throughout the blender.

The distribution of Mg stearate concentration in all sampling cores of the same experiment at a latter time is showed in Fig. 5b. These values fluctuate around 1.0% (between 0.5 to 1.5%) throughout the length of the cores. This finding indicates that Mg stearate is being distributed throughout the powder bed, and homogeneity will be reached when this fluctuation gets smaller.

4. CONCLUDING REMARKS

An experimental model was developed to successfully use NIR spectroscopy to determine homogeneity of powder blending. In this study, homogeneity was addressed by quantifying Mg stearate concentration in a ternary powder. The model that accounts for variability of the tracking component as well as the variability of the excipients, showed a good agreement between the calibrated and predicted values of the prepared samples for the calibration set. Such agreement is crucial to predict the unknown Mg stearate concentration from the blending experiments. NIR spectroscopy proved to be a well-suited technique to detect and quantify Mg stearate in terms of time efficiency as well as accuracy.

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REFERENCES

1. Alonso, M.; Alguacil, F.J. Dry mixing and coating of powders. Revista de Metalurgia Sep–Oct **1999**, *35* (5), 315–328.
2. Arratia, P.; Duong, N.; Muzzio, F.J.; Godbole, P.; Reynolds, S. Experimental and computational characterization of mixing and lubrication in Bohle Bin blender. Submitted to Powder Technology.

3. Blanco, M.; Coello, J.; Iturriaga, H.; Maspoch, S.; de la Pezuela, C. Critial review: near-infrared spectroscopy in the pharmaceutical industry. Analyst **1998**, *123*, 135R–150R.
4. Blanco, M.; Coello, J.; Eustaquio, A.; Iturriaga, H.; Maspoch, S. Development and validation of a method for the analysis of a pharmaceutical prepartion by near-infrared diffuse reflectance spectroscopy. Journal of Pharmaceutical Sciences **1999**, *88* (5), 551–556.
5. Harnby, N.; Edwards, M.F.; Nienow, A.W. Introduction to mixing problems. *Mixing in the Process Industries*, 2nd Ed.; Butterworth-Heinemann: Wiltshire, Great Britain, 1992, 16.
6. Johansson, M.E.; Nicklasson, M. Investigation of the film formation of magnesium stearate by applying a flow-through dissolution technique. Journal of Pharmacy and Pharmacology **1986**, *38*, 51–54.
7. Leinonen, U.I.; Jalonen, H.U.; Vihervaara, P.A.; Laine, E.S.U. Physical and lubrication properties of magnesium stearate. Journal of Pharmaceutical Sciences **1992**, *81* (12), 1194–1198.
8. Muzzio, F.J.; Robinson, P.; Wightman, C.; Brone, D. Sampling practices in powder blending. International Journal of Pharmaceutics **1997**, *155*, 153–178.
9. Podczeck, F.; Miah, Y. The influence of particle size and shape on the angle of internal friction and the flow factor of unlubricated and lubricated powders. International Journal of Pharmaceutics **1996**, *114*, 187–194.
10. Steffens, J.K.; Koglin, J. The magnesium stearate problem. Manufacturing Chemist **1993**, *64* (12), 16–19.
11. Sudah, O.S.; Muzzio, F.J. Quantitative characterization of mixing of free flowing granular materials in Tote (Bin)-blenders. Powder Technology, *in press*.
12. Wargo, D.J.; Drennen, J.K. Near-infrared spectroscopic characterization of pharmaceutical powder blends. Journal of Pharmaceutical and Biomedical Analysis **1996**, *14*, 1415–1423.