Determination of the Optimum Mixing Time for a Mixture of Lactose and Colloidal Silicon Dioxide

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Abstract □ The homogeneity of a mixture of colloidal silicon dioxide (CSD) and lactose is examined by quantifying the dependence of the CSD content on the mixing time. CSD concentration is determined photometrically as a blue silica–molybdic complex. Its deviation from the expected content is taken to characterize the mixture quality and the optimum mixing time. The conformity of this result with the flow properties of the same mixture is studied by measuring the dependence of the angle of repose on the mixing time.

1. Introduction

Mixing of powders is an important process in pharmaceutical production, e.g. in the manufacture of solid dosage forms. The quality of the final product especially with respect to content uniformity is primarily determined by the homogeneity of the mixture. The optimum mixing conditions have to be fixed carefully in each product development as they are strongly dependent on the properties of the mixture components. As a general approach we studied the mixing of lactose and colloidal silicon dioxide (CSD), two excipients widely used as fillers and flow regulators, respectively.

The flow property of a powder mixture is another parameter of utmost importance for effective production. Therefore we examined in addition the influence of mixing time of the two powders on their flowability.

The field of powder mixing has been treated by many authors. Poux et al.[1] compared the efficiency of several types of mixers used in pharmaceutical practice. Stange[2] and Johnson[3] studied the relevance of powder characteristics such as particle size, particle size distribution, and particle density for the segregation of the mixture. Speiser et al.[4] examined the influence of different mixer types on the mixing time and on mixture homogeneity.

Stiess[5] and Schweiger et al.[6] outlined in detail how to proceed in determining the optimum mixing time and how to perform the statistical evaluation.

For a given mixer and well-defined mixing intensity, the homogeneous distribution of the mixture components is dependent on the duration of mixing. To find its optimum, samples have been drawn from the mixture at defined time intervals. The content of tracer compound in these samples was determined. According to Stiess[5] the variance of tracer component is suitable to quantify the mixture homogeneity.

To assess the influence of the mixing time on the flowability of the mixture, how its angle of repose depends on the mixing time has been determined. Shape and height of a powder heap are controlled by the same forces as powder flowability.[7,8] Therefore, despite the fact that the range of its variation is limited, the angle of repose can be used to roughly estimate the flowability of a powder.

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Table 1—Specifications of the Material

	lactose G 200	Cab-O-Sil M5
density (g/cm^3)[13]	0.54	0.04
mean diameter[14]	43 μm	9 nm

2. Materials and Methods

2.1. Materials—Lactose monohydrate G 200 (Meggle GmbH, Wasserburg, Germany) and colloidal silicon dioxide Cab-O-Sil M5 (Cabot GmbH, Hanau, Germany) were mixed in a ratio of 99:1 (w/w). Specifications of the materials are given in Table 1.

2.2. Methods—*2.2.1. The Mixing Process*—To select an appropriate mixer we had to consider the physical properties of lactose and CSD.[1] Both are cohesive powders with considerable differences in particle size as well as in density. Under these conditions an Erweka MKS planetary mixer (Erweka GmbH, Heusenstamm, Germany) was found to be suitable (vessel volume, 5600 cm^3; filling volume, 75%; rotary speed, 60 rpm).

In the literature, mixing times ranging from 2 to 20 min are recommended when using planetary mixers.[1,9] It is general pharmaceutical practice to add colloidal silica as the last component to premixed bulk. The additional mixing time is a few minutes only. Therefore sampling was done after mixing times of 30 s up to 10 min.

2.2.2. Determination of the Minimum Number and Weight of Samples[5,6]—A minimum number of samples has to be drawn in order to allow a statistically significant characterization of the mixture. It is assumed that the composition of the samples follows a normal distribution.

If at a significance level of $\alpha = 0.10$ the empirical variance is required to be less than twice the population variance, then the minimum number of samples is calculated to be nine.

The minimum size of a sample is determined by the tracer compound. The sample has to be large enough to ensure that within the limits of statistical fluctuation the concentration of tracer compound is the same as in the bulk.

For our experiments we required that with a probability of 99.9% the composition of the sample deviates not more than 0.5% from the bulk composition. Under these assumptions the minimum number of particles per sample is calculated to be 3.8×10^7. This corresponds to a sample weight of 2.8 g. In the trials a mass of 5.0 g per sample was drawn in order to minimize the relative errors of the measurements.

The samples have been drawn in a systematic way at well-defined places within the mixing vessel (Figure 1). By means of a sampler samples 1−5, the upper samples, were drawn from the surface of the bulk, whereas samples 6−9, the lower samples, were drawn from the bottom of the mixer. The mass of the samples was not replaced.

2.2.3. Quantitative Determination of Colloidal Silicon Dioxide—Because in the mixtures the concentration of CSD was 1% only, this compound was used as tracer compound to assess the homogeneity of the samples.

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Table 2—Dependence of Content of Silicon Dioxide on Mixing Time (min) for the Three Test Series

	CSD content (mg/5.00 g sample)												
	test series 1				test series 2					test series 3			
	0.5 min	1 min	5 min	10 min	3 min	4 min	5 min	6 min	8 min	3 min	4 min	6 min	8 min
						Upper Sample							
1	82.6	81.1	54.2	14.3	102.1	73.5	26.5	36.7	51.9	44.2	52.3	57.3	45.9
2	162.8	71.7	45.9	47.8	54.3	31.3	57.8	54.2	18.3	65.1	58.4	34.4	6.5
3	41.6	59.5	58.5	58.8	71.3	78.3	56.0	46.0	21.2	21.3	46.2	66.5	49.1
4	68.8	88.1	34.9	41.1	52.6	58.3	59.3	70.4	31.8	30.8	43.1	53.7	44.2
5	31.3	113.6	38.2	40.5	74.7	24.0	62.8	54.5	50.0	53.9	36.2	53.9	76.5
						Lower Sample							
1	10.6	43.2	62.9	58.6	66.7	46.7	40.2	76.5	51.5	60.0	66.2	38.1	55.4
2	45.5	31.6	76.6	116.9	97.2	50.6	45.3	27.0	55.2	42.3	55.2	36.2	48.8
3	32.2	41.9	79.7	66.9	67.7	38.2	28.0	50.1	63.1	40.8	28.4	41.7	68.5
4	26.2	57.4	56.3	31.6	47.3	23.4	63.1	48.1	36.5	48.9	46.4	39.9	99.0
mean [mg][a]	55.7	65.3	56.4	52.9	70.4	47.1	48.8	51.5	42.2	45.2	48.0	46.9	54.9
standard deviation [mg]	45.7	26	15.4	28.8	18.9	20.1	14.4	15.3	15.8	13.7	11.5	11.3	25.5
variance [mg^2]	2090	676	238	828	359	404	207	233	250	189	133	127	651

[a] The theoretical content of silicon dioxide is 50 mg/5.00 g sample.

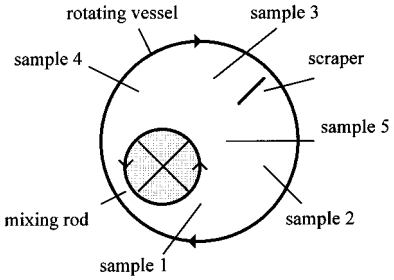

Figure 1—Schematic drawing of the planetary mixer. The places where the systematic sampling was done are indicated.

Silicon dioxide can be determined quantitatively by photometric determination of a blue silica−molybdic complex (molybdenum blue).[9]

Adding sodium molybdate to a basic solution of CSD leads to the formation of yellow molybdenum sililic acid, which under acid conditions is reduced by ascorbic acid to molybdenum blue. Its absorption at a wavelength of $\lambda = 810$ nm was measured with a Hitachi U-1100 spectrophotometer.

Under the conditions required for the formation of molybdenum blue, lactose produces a light yellow color. Therefore all photometric determinations have been carried out using a lactose solution as standard which was treated in the same way as the sample.

After defined mixing times (see Table 2) nine samples, each of 5.0 g, were drawn. Their content of CSD was trebly determined.

2.2.4. Determination of the Angle of Repose—The angle of repose δ was calculated according to eq 1.

$$\tan \delta = \frac{h}{r} \tag{1}$$

h is the height of the lactose heap formed on a plate with the radius r. Each measurement was repeated three times.

3. Results

3.1. Quantitative Determination of CSD—We studied the influence of mixing time on the homogeneity of our test mixture in three test series. The amounts of CSD as determined in the samples are summarized in Table 2. For a more precise determination of the optimum mixing time shorter time intervals have been chosen in the second and third series.

The variances of CSD in the samples are plotted against the mixing time (Figure 2). As can be seen at the beginning of the mixing process, these variances are very high, indicating poor homogeneity of the mixture. After 3 min of further mixing the variance decreases significantly. The mixture homogeneity has almost reached its optimum. After 8 min of mixing, however, an increase of the variance indicates the beginning of segregation.

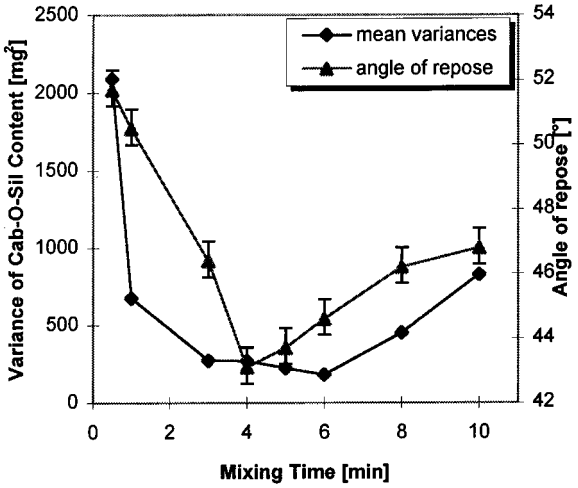

Figure 2—Mean variances of the CSD content (calculated from test series 1–3) and the dependence of the angle of repose on the mixing time.

3.1.1. Statistical Evaluation of the Test Series[10]—The equality of the variances is examined by performing a Hartley test. If all variances are included, the null hypothesis stating that all variances are equal has to be rejected. The variances determined at mixing times ≥3 min are found to be statistically equal. This means the mixture has reached its maximum homogeneity at a mixing time of 3 min.

3.2. Determination of the Angle of Repose—As can be seen from Figure 2, the course of the angle of repose as a function of mixing time runs almost parallel to the mean variances in content of CSD. With an optimally mixed powder, a significant reduction of the angle of repose is observed. This indicates a change from a cohesive to an almost freely flowing powder.

4. Discussion

The results of our study indicate that recommended mixing times ranging from 2 to 20 min[11] are not helpful.

With the given mixer in our test system consisting of lactose and CSD (99:1 w/w), optimum homogeneity was achieved after 3 min of mixing. Prolongation of the mixing time up to 6 min had no statistically significant negative impact on the homogeneity of the mixture. After 8 min of mixing, however, the first signs of segregation could be observed.

As seen in other studies,[12] the angle of repose is very sensitive to changes in flowability. The same can be confirmed by our findings. At the beginning of the mixing the powder is rather cohesive and becomes freely flowing at the optimum mixing time. The higher sensitivity of the angle of repose to changes in the homogeneity of our system can be explained by the fact that CSD shows a strong tendency to form agglomerates. As can be seen from Table 2 there are enormous variations in the content of CSD in the various samples taken at the same time. In contrast to the angle of repose, which measures the effective but not the actual content of CSD, the analytical method used in this study cannot differentiate between CSD in form of smaller or larger agglomerates.

Our findings demonstrate once more how important it is to determine the optimum mixing time for each formulation and equipment to be used.

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14. Particle size analysis was performed by means of laser light scattering with the Coulter LS 230 (Coulter Electronics GmbH, Krefeld, Germany).

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