Drug Development and Industrial Pharmacy, 24(10), 961–971 (1998)

RESEARCH PAPER

The Use of Particle Characteristics to Elucidate Mix Homogeneity in Binary Powder Blends

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ABSTRACT

A series of binary powder blends comprising microcrystalline cellulose (Avicel® PH101), α-lactose monohydrate, or anhydrous theophylline were prepared in order to investigate the ability of particle-characteristics measurements to express the homogeneity of the resulting mixture. It is postulated that fundamental physical characteristics, such as particle-specific surface area, true density, and size distribution, can be used to quantitatively ascertain mix homogeneity in routine pharmaceutical blending operations.

INTRODUCTION

Unit powder-blending operations are widely used in the pharmaceutical industry as an efficient and cost-effective means of constituent mixing during solid-dosage-form manufacture. Improper mixing of powders can lead to various quality deficiencies including variation in content uniformity, inadequate dispersion of coloring agents, and tabletting complications. However, difficulty frequently arises in the critical evaluation of blend homogeneity. The most widely used methodology employs the uniform sampling of a powder bed, with subsequent chemical quantitation of the constituents. When one or more of the constituents of interest do not easily lend themselves to this approach, other parameters must be exploited.

Routine galenical characterization of powders in industrial pharmaceutical operations typically involves the measurement of derived properties of powders. These properties exist only as a result of the interplay of a collection of particles, which can involve such attributes as powder flow, powder compressibility, porosity, and bulk density. As a result, the derived properties of powders also reflect the complex interaction of interparticle forces,

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and may not be suitable as markers of blend homogeneity. Therefore, the focus of the present study was to examine the extent to which fundamental particle properties, such as surface area or size distribution, can be correlated with the extent of constituent dispersion during powder blending. The study was facilitated by use of the two most common pharmaceutical excipients (1): microcrystalline cellulose and α-lactose monohydrate, as well as by the well-characterized active ingredient anhydrous theophylline. A goal of this research is to establish a rationale that adequately describes the observed physicochemical properties of a series of binary powder blends involving these materials.

BACKGROUND

Typically, mixing had been regarded as a random-motion operation that achieves random distribution of particles by simply "shuffling" large and small particles in a confined space. This approach was conducive to the development of many statistically based expressions used to describe the degree of homogeneity of powder blends comprising two or more components that were assumed to consist of spherical, independent particles (2,3). Ensuing research in this area identified the problems in using independent spheres to model particulates during powder mixing (4,5); notably, electrostatic and cohesion forces at play during mixing processes are responsible for the segregation of powders. As a result, complete random mixing of powders is rarely accomplished in practice. The complexity inherent in mathematically representing this type of dynamic system necessitated more pragmatic approaches to ascertaining mix homogeneity.

There exist in the scientific literature a number of novel approaches to assessment of mix homogeneity when chemical analysis is not an option. These approaches have typically centered around the identification of a physicomechanical parameter that is adequately sensitive to changes in the extent of particle mixing during the course of a blending operation to be used as a measure of mix homogeneity. Chapuis and Pouliot (6) utilized the x-ray diffraction profile of bentonite in montmorillonite sand as a means of monitoring mix homogeneity of these two materials. In a similar fashion, the Recognition Index, derived from the near-infrared spectrum of a mix component in comparison with a derived library of incompletely mixed material, provided a means of probing pharmaceutical powder granulations (7). These approaches have in common the identification of particle characteristics resulting from measurements at the molecular level. The possibility of exploiting other fundamental particle characteristics, determined instead from physicochemical measurements, is worthy of exploration as a means of quantifying powder-blend homogeneity.

Staniforth et al. (8) reviewed and evaluated 11 different methods of testing the homogeneity of powder mixes in terms of their usefulness as routine quality-assurance procedures for investigating drug-content uniformity. Of these methods, two were considered to be of merit: one based on a powder-flowability test and the other based on a vibration stability/segregation test. The test results could be used to correlate the mechanism of a given powder system with theoretical data obtained from the individual ingredients. These tests inherently reflect the effect of changes in bulk density on the technologic potential of the resulting powder mix. Indeed, the use of bulk-density measurements of the ensuing powder mix in relation to the bulk density of the pure constituents may be a useful means of directly assessing mix homogeneity. A number of different terms for powder density are reported in the scientific literature, and for clarity the following can be defined (9): bulk density, ρ_{bulk}, as the mass of particles composing a bed divided by the volume of the bed; tapped density, ρ_{tap}, as an extension of this measure after subjecting the powder bed to abrupt tapping while in a container; particle density, ρ_{par}, as the mass of particles divided by the envelope volume of the particles; and true density, ρ_{true}, as the mass of particles divided by the solid volume. Additionally, other parameters, such as total porosity, ε, can be calculated from these density measurements. The total porosity is a combination of the void volume between particles (interparticle volume) and the pores within the particles (intraparticle volume), and can be calculated as (10):

$$\varepsilon = 1 - \frac{\rho_{bulk}}{\rho_{true}} \quad (1)$$

Based on the optimum theoretical packing, either cubic or tetrahedral, of uniform, spherical particles, the solid fraction of a loosely packed powder would be 0.53, while that of a closely packed powder would be 0.74 (11). However, as previously indicated, powders are seldom monomodal or consist of spherical particles, so that actual powder blends can exhibit solid fractions over a wider range, particularly when the particle sizes of constituent materials are significantly different. In this case, small particles may occupy the interstitial spaces between large particles, and greatly increase the solid fraction per unit volume. On the other hand, if a constituent powder is composed of particles of extremely small diameter, then

surface-adhesion forces predominate, resulting in particle agglomeration. Powder behavior of this nature leads to difficulty in properly dispersing the powder in mixing operations. Anhydrous theophylline, used in this study, is an example of this latter type of powder.

Particle shape has also been shown to influence bulk densities (12,13). Many pharmaceutical powders have particle shapes that are not conducive to bulk interparticulate movement during blending. These materials may therefore undergo static heaping within a localized area of a powder mix, as a result of their packing characteristics. Indeed, Zou et al. (14) have shown the utility of defining an equivalent particle-packing diameter in facilitating prediction of the porosity of powder beds consisting of spherical and nonspherical particles. They concluded that the initial powder-bed porosity, and thus the bulk density, of binary mixtures decreased with increasing sphericity of particles.

The previous discussion introduced the problems associated with using measurements of derived powder properties, such as bulk density and porosity, to quantitate powder-blend homogeneity. These measurements tend to be confounded by fundamental particle properties such as particle size and particle morphology. Therefore, selecting measurement parameters that directly reflect fundamental particle properties may provide better predictive capabilities with respect to ascertaining powder-blend homogeneity.

In this respect, particle true density measurements and specific surface-area determinations may provide some insight into constituent dispersion within a binary blend, provided that the analyses are precise and accurate. Since true particle density is the density of the particle material, excluding pores and interparticle voids, it should accurately represent the quantity of material occupying a given volume. Accordingly, particles of different constituents but residing in the same unit volume can be quantitated without regard to particle shape, by simply relating the composite true mass occupying the unit volume to the true mass per unit volume of the pure constituents. Specific surface-area measurements, which quantify, relative to particle mass, the particle surface area accessible to an adsorbing gas, provide a similar useful determination of dispersion.

Presumably, particle size can also be of use in homogeneity determinations if the entire distribution profile is exploited. This approach is used in statistical analysis, through calculation of the skewness and kurtosis of a population distribution, which measure the departure from normality of the distribution. Since particle-size is typically not normally distributed, log-normal transformation of the data is used to aid in the data analysis. However, a single scalar quantity, such as these statistical moments, fails to express the particle mass frequency information inherent in a distribution. Stated more simply, if a 50% w/w ideal blend of two constituent powders is achieved, then with ideal sampling it will be found to consist of half of the particle-number distribution of each constituent.

MATERIALS AND METHODS

Materials were obtained from various commercial suppliers as follows: Avicel® PH101, microcrystalline cellulose (Lot number 6551), was obtained from FMC Corporation, Newark, DE. Pharma 200/70, α-lactose monohydrate (Lot number 45097) was obtained from S. A. du Sucre de Lait, Sains du Nord, France. Anhydrous theophylline (Lot number 223400) was obtained from Boehringer-Ingelheim, Ingelheim, Germany.

Preparation of Mixes

One-kilogram binary mixes of each of the three test ingredients (Avicel PH101, α-lactose monohydrate, anhydrous theophylline) were produced in a Turbula Type T2C (Bachofen AG, Uster, Switzerland) reciprocating tumble mixer set at 70 rpm for 5 min. The binary blends containing theophylline were restricted to 50% w/w or less of this component so as to reflect plausible industrial processes. The mixer container was charged with an accurately weighed fraction of each ingredient (Fig. 1), which had been previously passed through a 1-mm mesh-size stainless steel screen to eliminate material aggregates.

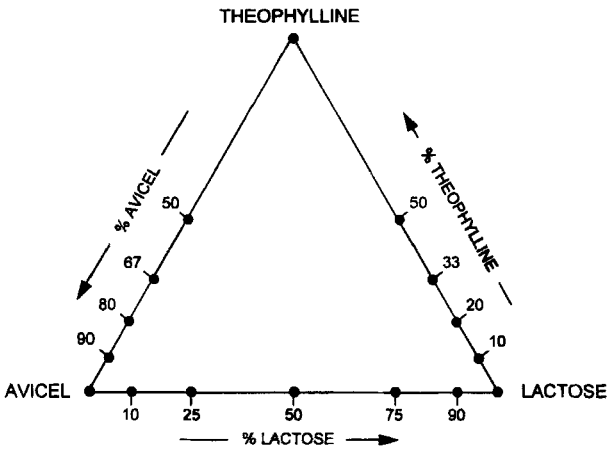

Figure 1. Binary powder blends under consideration.

Particle Morphology

Scanning electron microscopy (SEM) (Scanning Electron Microscope Model S2500 Hitachi, Tokyo, Japan) was used to assess the surface topography and texture of the pure materials. Samples were mounted on the SEM stage and were 80% gold/20% palladium sputter-coated at 15 mA for 120 sec at 0.05 mbar.

Density

True Density

Gas pycnometry (AcuPyc 1330, Micromeritics Instruments Inc., Norcross, GA) was used to determine the true density of the powders and blends. Known quantities of samples were degassed under vacuum for 24 hr at room temperature, after which 10 repetitive purge/measure cycles were performed before recording the result. The analysis was performed on three independent samples. Helium was used as the displacement gas because of its preferential small molecular size.

Apparent Density

The evolution of the apparent density of a powder bed in a volumetric cylinder subjected to successive vertical shocks (taps) was measured according to the method outlined in the Pharmacopée Française, X^e (V.5.5.4), utilizing the Erweka Model SVM2 unit (Erweka GmbH, Heusenstamm, Germany). The reduction in powder volume is effected by primary particles rearranging into closer contact on each tap of the bed. This particle flow and consolidation can be quantitated by using the empirical relationship proposed by Carr (15):

$$\%C = \frac{d_\infty - d_0}{d_\infty} \cdot 100 = \frac{V_0 - V_\infty}{V_0} \cdot 100 \qquad (2)$$

where d_0 is the powder mass per V_0, the initial powder volume, and d_∞ is the powder mass per V_∞, the final powder volume.

Surface Area

The surface areas of the powders and blends under study were determined by the gas-adsorption technique (Gemini 2360, Micromeritics Instruments Inc.). The method is based on the Brunauer, Emmett and Teller (BET) monolayer adsorption theory of a gas on a solid surface at reduced temperatures. Nitrogen was used as the condensable gas after the samples had been degassed under vacuum for 24 hr at 50°C (VacPrep 61, Micromeritics Instruments Inc.). Samples with less than 1.0 m^2/g of total surface required careful adjustment of the reference void volume in order to obtain reproducible results.

Particle Size

Separation of particles on the basis of effective particle volume was accomplished by analysis of diffracted laser light passing through an air suspension of the powder under study (Malvern Mastersizer, Malvern Instruments, Ltd., Malvern, UK). The diffraction pattern is mathematically interpreted according to fundamental theory, which assumes a spherical particle geometry.

RESULTS AND DISCUSSION

Generally, particle-level properties such as size, morphology, and surface rugosity are determined in a qualitative manner from observational analysis. Properties of particle assemblies (i.e., powders) tend to be application oriented, and comprise characteristics such as size distribution, apparent density, texture, compressibility, flowability and porosity, requiring the use of tests in their determination. Thus, in all determinations of particle and powder physicomechanical parameters, a fundamental understanding of the physical principles employed by the measuring apparatus is paramount.

The concept of mix quality is difficult to assess since it involves a number of contributing factors arising not only from the physicochemical properties of the mixed powders but also from the conditions used to generate the mix, as well as the methods used in sampling (16). An excellent review of some of these concerns has been published by Fan et al. (17). Thus, the goal of our present research is to examine the utility of nonconventional physicochemical analysis in assessing powder dispersion during pharmaceutical blending operations.

Constituent Profiles

Physical characterization of the initial constituents of the binary mixtures examined in our study appears in Table 1. The span of an order of magnitude between the mean particle size of the constituent materials is problematic in blend operations, and typically contributes to constituent segregation. Additionally, particles that are uniform and small in size generally give rise to a lower bulk density, as shown here by theophylline. This characteristic, as well as the effect of particle morphology on pow-

Table 1

Physical Characteristics of Powders Studied

	Theophylline Anhydrous	α-Lactose Monohydrate	Avicel® PH101
True density, ρ_{true}, (g/cc)	1.479	1.534	1.534
Bulk density, ρ_{bulk}, (g/cc)	0.267	0.844	0.303
Particle size, d_v, (μm)			
Mean	23	243	85
Median	17	236	71
Span*	2.32	1.68	2.00
Surface area (m^2/g)	0.722	0.171	1.166
Carr index, C, (%)	34.5	13.9	23.5

*Span is the measure of the spread in the d_v distribution, and is calculated as: $\frac{d_{90\ \text{percentile}} - d_{10\ \text{percentile}}}{d_{50\ \text{percentile}}}$

der flowability, is aptly reflected in the Carr consolidation index for the constituents. By contrast, it does not follow that the small mean particle size of theophylline presupposes it to have the largest specific surface area of the constituents studied. In fact, the constituent Avicel has the largest specific surface area, by virtue of its known appreciable surface rugosity and intragranular porosity. As a result, there does not appear to be a direct correlation between the bulk and true density values of each constituent material. Evidently, particle morphology plays a crucial role in the processes of consolidation of these powders, and is also likely to affect their blending facility.

Particle Morphology

The direct observation of particles of blend constituents reveals a number of pharmaceutically important characteristics with respect to crystal habit, surface texture and rugosity, and geometry, as noted in Fig. 2. It is evident from granulometry that the lactose and Avicel samples are widely dispersed, with evidence of large particles (>100 μm) as well as extremely small particles. Additionally, the granules of lactose are obviously angular in shape, whereas those of Avicel are acicular. Observation of Avicel particle surface morphology reveals evidence of pores and surface fissures, as predicted by the relatively large surface area. By contrast, the particles of anhydrous theophylline appear to be platelike, clean, and free of defects.

These observations have serious implications with respect to instrumental analysis of particle size, since the particle shapes are notably different. Unless the particles

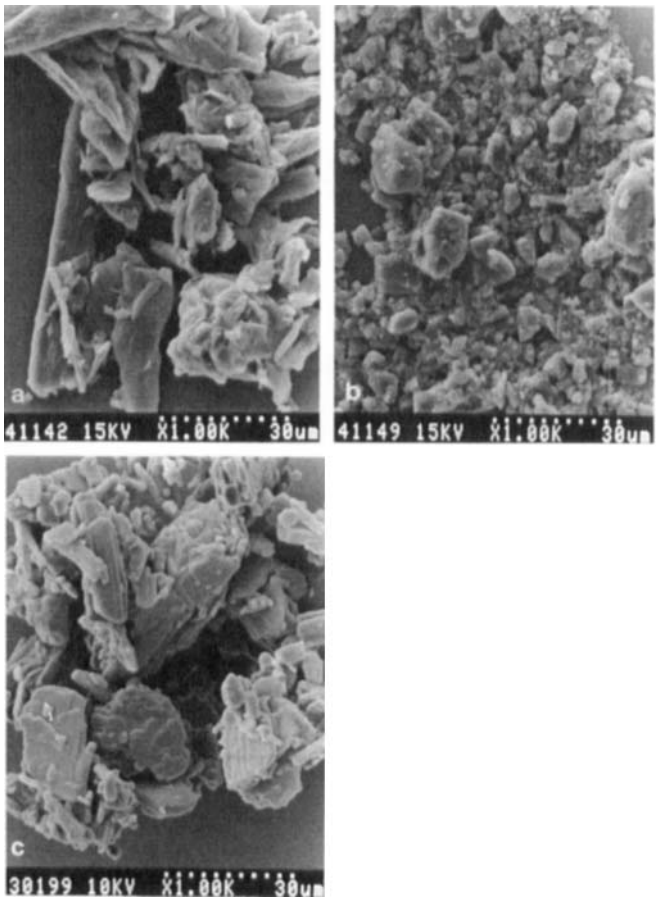

Figure 2. Scanning electron micrographs of constituent powders. (A) Avicel PH101; (B) α-lactose monohydrate; (C) theophylline monohydrate.

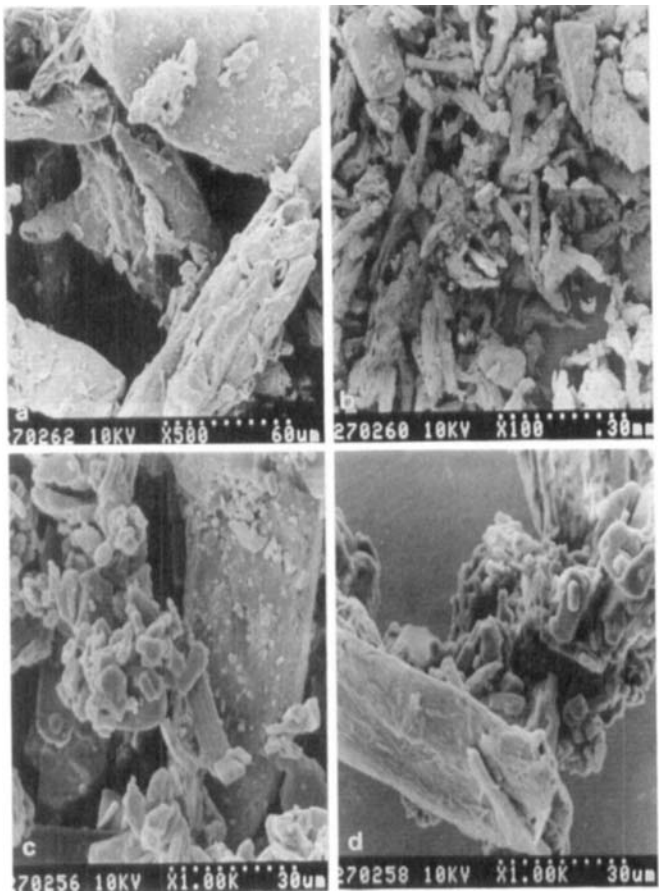

Figure 3. Scanning electron micrographs of 50% binary blends. (A and B) Avicel® PH101–α-lactose monohydrate; (C) α-lactose monohydrate–theophylline monohydrate; (D) Avicel® PH101–theophylline monohydrate.

are perfectly spherical, there is no unique dimension for their measurement, and the assessment of size will be subjective. Furthermore, differences in crystal habit may have an effect on the distribution of particles within binary mixtures.

Generally, successful homogeneous blending of powders is difficult if there is a large difference in the constituent particle sizes. This effect is alleviated if ordered mixing takes place by adsorption of small particles onto the surfaces of large particles. Electron micrographs of 50% binary blends (Fig. 3) do not show evidence of this surface-adsorption phenomenon. As a result, these powder blends are not likely to withstand excessive process handling without undergoing some degree of demixing. The application of suitable physical measures to assess mix homogeneity is advantageous in the process monitoring of this type of blend.

Density

In Fig. 4, the bulk and tapped densities of the various binary blends are shown as a function of the relative pro-

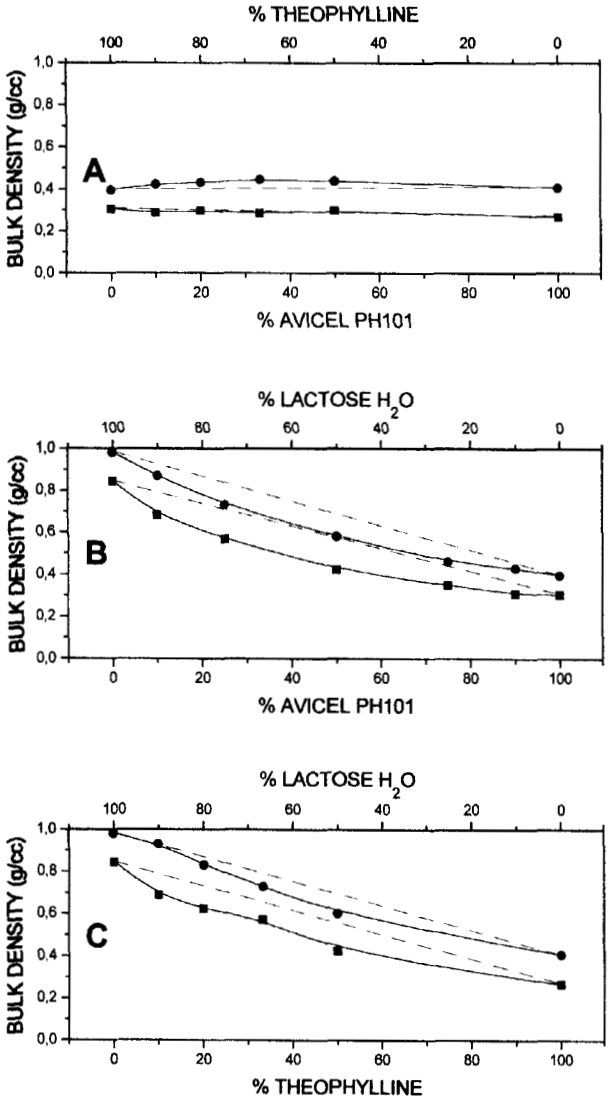

Figure 4. Bulk density and tapped density determinations of binary powder mixes (■) Bulk density; (●) tapped density after 1250 taps; (---) linear interpolation between the pure constituents. (A) Avicel PH101–theophylline monohydrate; (B) Avicel® PH101–α-lactose monohydrate; (C) α-lactose monohydrate–theophylline monohydrate.

portion of each blend constituent. The influence of particle morphology on the resulting density measurements reaffirms the need to consider this effect in powder-manipulation operations. The results indicate that in no case is the density of the binary mixture simply the sum of the relative proportions of the pure constituent densities. Given that an order of magnitude separates the mean particle size of Avicel and theophylline and that of lactose and theophylline, it is interesting that there does not appear to be a maximum in the measured bulk density of the binary mixes. This is contrary to previous observations (18), which would suggest that small particles of theophylline should fill the void between the larger particles of the second component, producing maximum packing at about 70%–80% of the coarser powder in the mixture (19). However, Podczeck and Sharma (20) have shown that particle shape of the individual components in a binary mixture significantly affects volume reduction in powder mixes. In the case of the binary blends containing Avicel [Fig. 4(a) and 4(b)], added angular particles of theophylline or lactose may be held apart as a result of the bridging capabilities of the acicular Avicel particles. As the proportion of the more dense lactose increases in the blend [Fig. 4(b)], the weak Avicel bridges collapse, resulting in a substantial increase in the observed bulk density. In the case of the theophylline/lactose binary blend [Fig. 4(c)], the wide dispersion in the lactose particle size, as noted in the scanning electron micrographs, serves to minimize the effect of the increasing proportion of small, platelike theophylline particles in the blend. Evidently, no simple relationship between component bulk density and mix homogeneity exists at this level of measurement.

Assessment of primary particle characteristics may provide more possibilities. Figure 5 shows the results of true density measurements on the same powder blend. Whereas the bulk density of theophylline and of Avicel was essentially identical, the true particle density of these materials, as noted in Fig. 5(a), is appreciably different, so as to be of some predictive value. The contrary is true for the bulk and true densities of Avicel and lactose. Nevertheless, the resulting linear relationship between the percent constituent proportion and the true density is well correlated for the various blends. The accuracy of the measurements can be seen with respect to the results obtained for accurately weighed samples containing each component at the theoretical proportion. Of particular interest is the good correlation of Turbula-blend samples with the corresponding weighed samples. The data reflect the excellent blend homogeneity of the mixes. The results

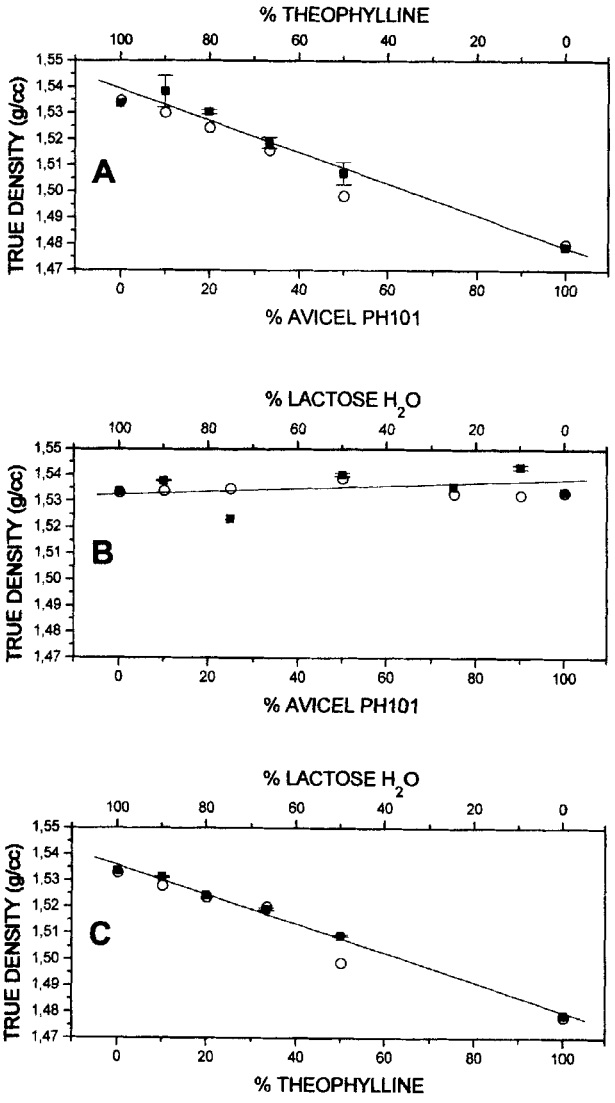

Figure 5. True density determinations of binary powder mixes. (■) Blended bulk sample; (○) proportionally weighed sample. (A) Avicel® PH101–theophylline monohydrate; (B) Avicel® PH101–α-lactose monohydrate; (C) α-lactose monohydrate–theophylline monohydrate.

indicate that this method of assessing mix homogeneity can be applied in the routine analysis of mix homogeneity.

Interestingly, the overall tendency of the bulk-density curve in Fig. 4 for each binary blend is maintained even after repeated tapping of the bulk (ρ_{tap}). When this is contrasted with the obvious trend differences in the respective true density curves (Fig. 5), it is clear that the pres-

ence of different-sized particles with different true densities is not by itself enough to facilitate packing into the theoretical dense bulk. Particle morphology, and specifically rugosity and its effect on particle consolidation, are the predominant characteristics here.

Specific Surface Area

A series of preliminary experiments were done to identify the optimum sample-conditioning parameters for the pure constituents in our blends. Since the surface of solid materials may contain adsorbed contaminants such as moisture, the powders were subjected to a degassing phase prior to surface-area analysis. This pretreatment consisted of maintaining the samples at a specified, elevated temperature under vacuum for a predefined duration. In the case of organic compounds, it is imperative that the pretreatment stage not perturb the material in any way. Both α-lactose monohydrate and Avicel contain approximately 5% w/w of associated water, which may be affected by temperature conditioning. Pharmaceutical modification of lactose monohydrate to the anhydrate can begin at 120°C (21). For this reason, the conditions of sample pretreatment were strictly followed so as to facilitate the comparison of results.

The results of the specific surface-area measurements made on the binary blends of the substances used in the study is graphically represented in Fig. 6 as a function of the mass proportion of the constituents in the blend. The values for the pure compounds are in good agreement with literature data (22), and indicate that an arithmetic calculation of the specific surface area of these blends can be undertaken on the basis of the values for the pure constituents. Additionally, the results demonstrate the ability to obtain reproducible measurements of specific surface area through nitrogen adsorption with blank referencing for materials of low surface area.

Mix homogeneity may be quantitatively assessed by evaluating the magnitude of the standard deviation for a number of sample determinations, as well as the departure from the theoretical linear liaison between the constituents.

Particle-Size Distribution

Granulometric distributions of the pure constituents of a powder blend as measured by laser diffraction are characteristically monomodal for all materials. The results are displayed in terms of a percent volume distribution, from which it is more useful to estimate the mean particle size, d_v. Because only a small sample size is required to effect

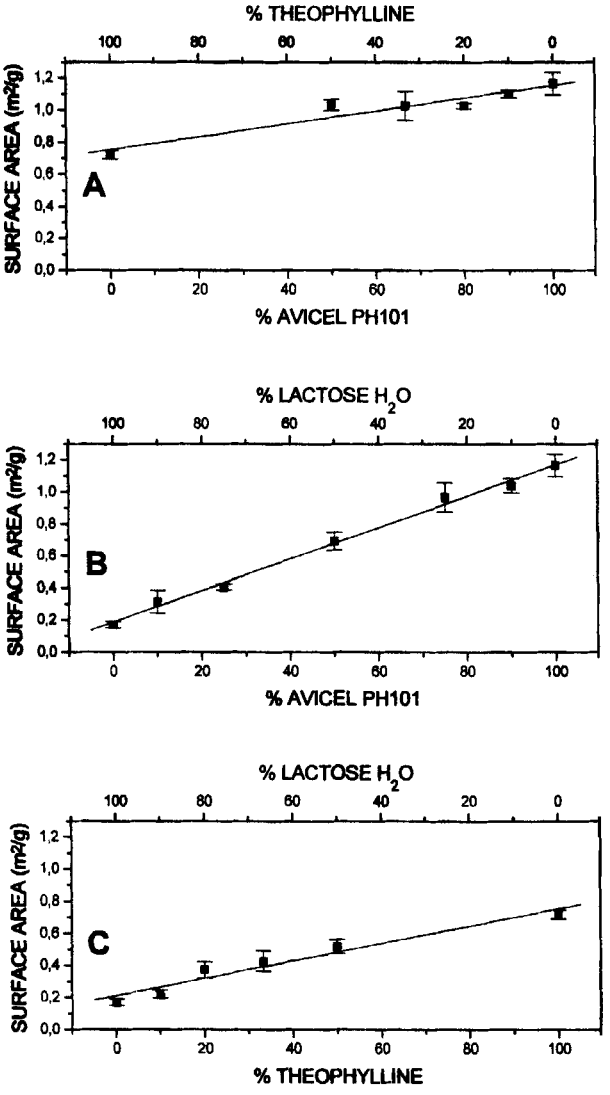

Figure 6. Specific surface-area determinations of binary powder mixes. (A) Avicel PH101–theophylline monohydrate; (B) Avicel® PH101–α-lactose monohydrate; (C) α-lactose monohydrate–theophylline monohydrate.

the measurement in this technique, sample segregation is an important consideration and important source of error in the resulting analysis. In practice, equivalent diameter is used to describe the diameter of a particle. This is defined as the diameter of a sphere with the same properties as the particle under consideration; i.e., the same volume, the same projected surface, the same rate of sedimentation, and so forth. Nevertheless, the data in Table 1 confirm the significant differences in particle-size distribution for the pure substances used in our study. These

differences are further accentuated when binary blends are produced from these materials. As expected, the granulometric distributions of some of the blends show obvious bimodality (Fig. 7), which complicates traditional granulometric analysis. It is apparent that "mean particle size" for this type of powder blend is an inappropriate parameter for properly characterizing the blend.

Despite the constraints of the instrumentation used in calculating the equivalent spherical volumes of particles, the results show surprising linearity when size weighting is applied (Fig. 8). Although more robust analysis of particle-distribution profiles can be undertaken (23), the simplicity of this approach makes it useful for rapid monitoring of the progression of powder mixing during blending operations. It is particularly useful when a significant difference exists between the mean particle size of the blend constituents. The basis of the size-weighting calculation is the recognition that the distribution function of the size parameter of a population remains the same irrespective of the definition of the size parameter. For acicular Avicel

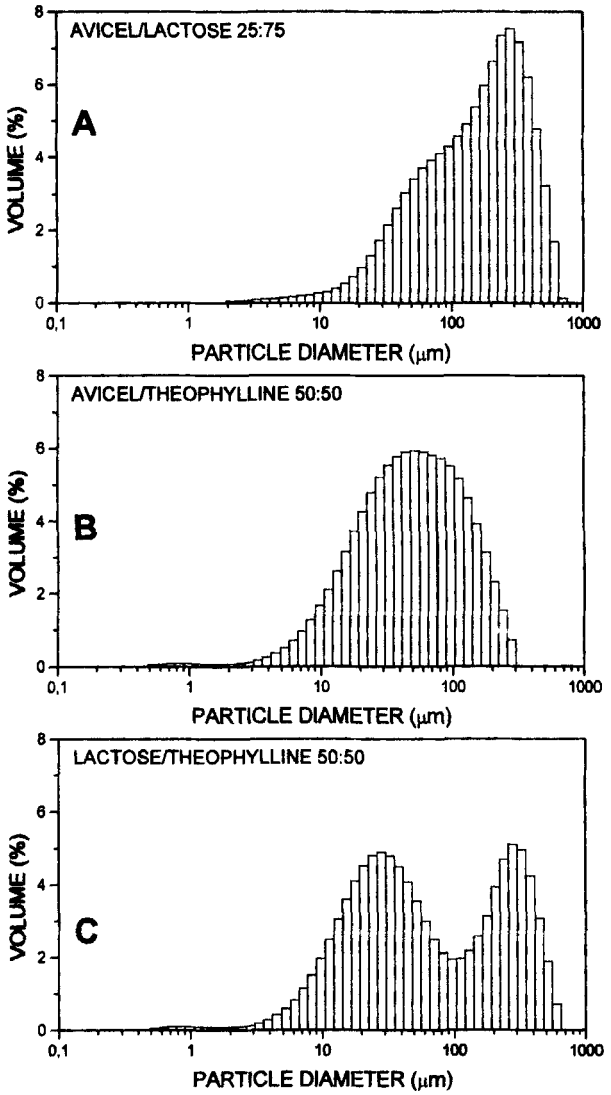

Figure 7. Particle-size distribution of binary powder mixes. (A) Avicel PH101–theophylline monohydrate, 50:50 w/w; (B) Avicel PH101–α-lactose monohydrate, 25:75 w/w; (C) α-lactose monohydrate–theophylline anhydrate, 50:50 w/w.

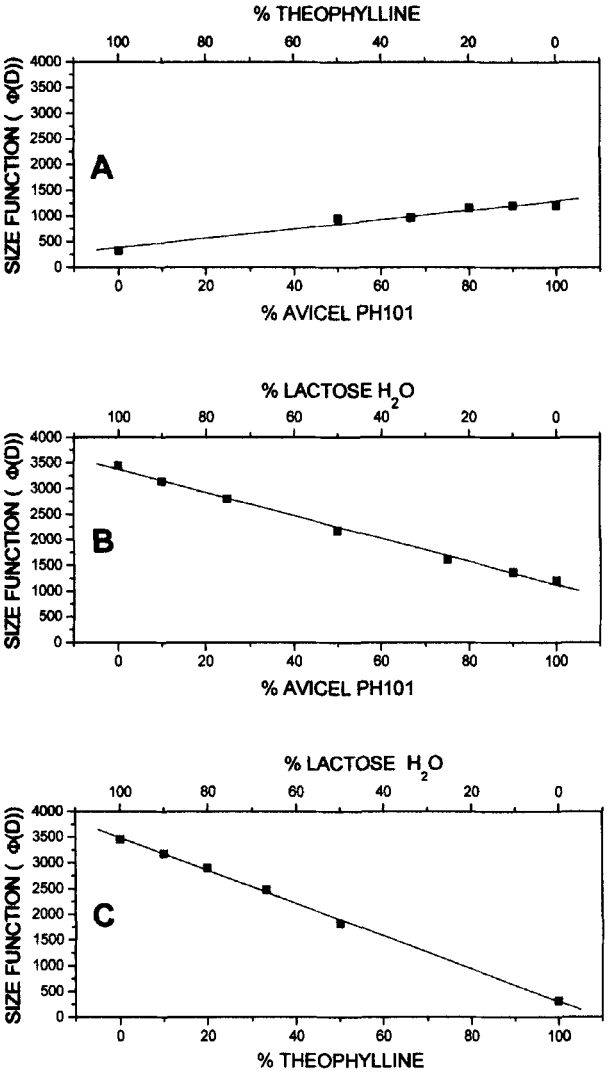

Figure 8. Calculated particle-size frequency function in relation to percent mass proportion of the constituents. (A) Avicel PH101–theophylline anhydrate; (B) Avicel PH101–α-lactose monohydrate; (C) α-lactose monohydrate–theophylline anhydrate.

particles, this is of particular importance, since the particle-size distribution obtained by laser diffractometry provides useful relative size information regardless of the actual particle geometry.

Thus, a modified size-frequency parameter can be computed for each size-distribution curve by using appropriate size "slices." A particular size slice is defined as the percent normalized volume of particles that have a diameter in the interval $[d_v - d_v + \Delta d_v]$. The use of absolute size in the calculation will necessarily skew the results in favor of large-diameter particles; however, use of the size interval, Δd_v, minimizes this effect:

$$\text{Size-weighting parameter } (\Phi_d) = \sum_{i=1}^{n-1} (dv_{i+1} - dv_i) \cdot f_i \quad (3)$$

where $(dv_{i+1} - dv_i) = \Delta d_v$, and f_i is the percent normalized volume of particles in the Δd_v size slice. Since granulometric data typically display a log-normal distribution, the range of the size interval is selected such that

$$\log(dv_{i+1}) - \log(dv_i) = \text{constant} \quad (4)$$

Thus, the most complete description of the particle population is obtained by using the entire size-distribution curve of a powder sample. The plot of this parameter as a function of percent constituent (Fig. 8) indicates that mix homogeneity was achieved for all blends in the present study.

Statistically, a chi-square test can be used to evaluate the utility of applying an arithmetic proportional weighting to component-size distributions according to the mass proportion of each component in a binary blend (Fig. 9). By comparing the expected, calculated particle-size frequency to the actual frequency for each size interval, and summing over all intervals, a chi-square statistic is obtained that can be used to quantitatively express the departure of the powder mix from theoretical blend homogeneity. The results in Table 2 show that in the studied binary blends, the obtained particle-size distribution did not differ significantly from the calculated distribution ($p \geq 0.05$), indicating that blend homogeneity was indeed achieved. Figure 9 graphically illustrates this modest departure for a mix, which resulted in a relatively large chi-square value. However, the highest chi-square values were obtained for blends of Avicel and theophylline, reflecting the potential mix difficulties associated with materials of different particle morphologies, and for blends of lactose and theophylline, reflecting the potential mix difficulties associated with materials of largely differing mean particle size.

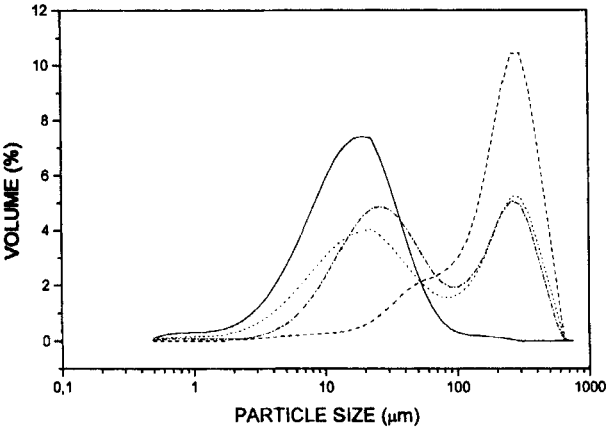

Figure 9. Proportional weighting of particle size distribution of the constituents in terms of their percent mass proportion in a 50% binary blend of theophylline anhydrate- and -α-lactose monohydrate (---), where (-·—·-) denotes actual blend distribution and (....) denotes calculated blend distribution.

Table 2

Chi-Square Parameter of Powder-Mix Size Distributions Obtained by Mass Proportional Calculation

Mass Proportion (%)	Theophylline	Avicel PH101	Theophylline
0	—	—	—
10	3,12	0,458	1,14
20	4,45	—	2,76
25	—	0,856	—
33	2,56	—	3,77
50	10,9	1,72	8,43
75	—	3,43	—
90	—	3,52	—
100	—	—	—
	Avicel PH101	Lactose	Lactose

CONCLUSIONS

The utility of physicochemical measurement of fundamental particle properties as a means of assessing mix homogeneity in model binary blends has been demonstrated. The confounding effect of particle size and shape on powder characterization is avoided by considering the particle-level properties of powder assemblies. This approach has merit for routine assessment of powder mixes during pharmaceutical powder-handling operations.

ACKNOWLEDGEMENTS

The authors are grateful to Elf Aquitaine Inc., France, and Sanofi Winthrop France for financial assistance, and to Jean Battini, Micromeritics, France, S. A, Stéphane Rouquette, Malvern Instruments S. A., and Miguel Viana, ENSCI, Limoges, for related discussions and determinations.

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