Anal.—Calcd. for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.27. Found: C, 68.09; H, 8.92; N, 5.62.

Attempted Isomerization of Deoxycycloheximide (III).—A solution 0.10 Gm. (0.38 mmoles) of deoxycycloheximide (III) and 80 mg. (0.41 mmoles) of *p*-toluenesulfonic acid was refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature, then poured onto ice. After the ice had melted, the mixture was filtered, and the filtrate was extracted with chloroform (4 × 30 ml.). The organic layer was washed with saturated solution of sodium bicarbonate (2 × 25 ml.), water (25 ml.), and dried with anhydrous magnesium sulfate. After filtration the volatile materials were removed *in vacuo;* the semisolid residue on crystallization from methanol and water gave 0.05 Gm. (50%) of deoxycycloheximide, m.p. 110–112°; $\bar{\nu}$ in cm.$^{-1}$ (KBr), 3200 and 3100 (NH); 1730, 1700, and 1680 (C=O). One recrystallization of the crude material from methanol and water gave a pure sample of deoxycycloheximide, m.p. 114–115°, mixed m.p. 112–114°, with an authentic sample of deoxycycloheximide.

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Segregation Kinetics of Particulate Solids Systems I

Influence of Particle Size and Particle Size Distribution

By JAMES L. OLSEN† and EDWARD G. RIPPIE

Rates of segregation of initially randomly distributed mixtures of steel spheres of various sizes have been studied. Extent of segregation was determined by sampling the entire system and expressed as the standard deviation of the sample compositions from the mean composition of the system. The several idealized systems studied showed apparent first-order kinetics, and rate constants were determined as a function of particle size and particle size distribution. Segregation in these studies proceeded to an equilibrium state in which mixing and unmixing effects were balanced.

Mixtures of solids are involved in many processes of industrial and technical importance. The glass, ceramic, paint, powder metallurgy, cement, and pharmaceutical industries are among those in which control of systems of solid particles is essential for the production of an acceptable end product. Such general characteristics as particle size distribution, "average shape," pore size, tendency to flow, and uniformity of composition are of prime importance (1).

Since the manufacture of tablets is generally accomplished by the compression of granulated or powdered solids, uniformity of dosage depends to a large extent on the uniformity of mixing of the granulation. The problem of maintaining a uniform mixture is particularly acute where many powdered ingredients having different size distributions, densities, and shapes are to be combined in a single tablet.

Solids mixing as a unit operation has received most attention in the literature in connection with specific types of mixers. Rate equations allowing approximate calculations of the time of mixing necessary to achieve a complete mix have been derived by several workers (2–5). Again, these studies primarily reflect the character of a specific mixer rather than the nature of the mechanisms of mixing and unmixing in general. It is thought, however, that mixing proceeds to a state wherein processes (convection, shear, and diffusion) leading to a random mix balance the tendency to segregate (5). Mixers are adjusted so that this segregation effect is minimized; however, subsequent handling of the mix may render it unsatis-

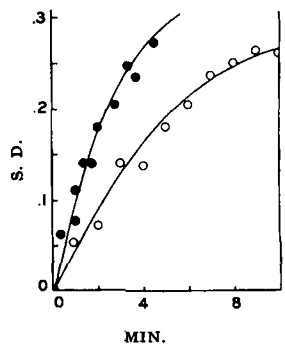

Fig. 1.—Plot of the standard deviation of a binary system *vs.* time of agitation. Solid points are at a 1:1 weight ratio of 8/32 *vs.* 3/32 in. steel balls. Open points are at a 1:1 weight ratio of 6/32 *vs.* 3/32 in. steel balls.

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factory for the next step in the process, due to induced unmixing.

Since, to our knowledge, no fundamental studies have been undertaken to determine the mechanisms of segregation or the factors which influence it, we have carried out preliminary work in this area. Results indicate that valuable information can be obtained on batch unmixing as well as on the nature of interparticulate interactions in a solids system.

THEORY

It is necessary in a study of this kind to determine the extent to which segregation has occurred so that a meaningful determination of unmixing rate can be made. Several methods of quantitatively assigning a "degree of mixing" to a particulate solids system have been used (6). While no single system is exclusively employed, we have found the standard deviation, as used by Weidenbaum (3), to be most satisfactory, since it is directly related to the relative numbers of particles which can be considered mixed or unmixed.

Consider a system consisting of two types of particles differing from each other only in size. The same treatment applies to particles differing by any other variable or combination of variables, such as density and shape. The standard deviation of the system equals

$$S = \sqrt{\frac{\Sigma f_i(u - X_i)^2}{n}}$$

where f_i is the weight of the i sample, u is the weight fraction in the system of the size particle being followed, X_i is the weight fraction in the i sample of the size particle being followed, and $n = \Sigma f_i$ which is the total weight of the system. For computational purposes this may be converted to

$$S = \sqrt{\frac{\Sigma f_i X_i^2}{\Sigma f_i} - \frac{(\Sigma f_i X_i)^2}{(\Sigma f_i)^2}}$$

In such binary systems, either component may be analyzed for without changing the calculated standard deviation. However, with systems containing more than two components, the standard deviation obtained will depend on the component followed and will reflect the degree of segregation of that component relative to the remainder of the system. Standard deviation has been selected as an index since it depends only on the extent to which the system deviates from a perfectly random state and on the size of the samples into which the system is divided. If proper selection is made of the sample size, the standard deviation is a reliable measure of the relative number of "mixed" and "unmixed" particles in the system and can serve as a basis for the study undertaken here.

EXPERIMENTAL

General Considerations.—Steel spheres of various sizes have been used as model systems in these studies so that the factors contributing to segregation can be determined without the complicating shape effects expected with nonspherical particles. The studies were carried out by a general procedure developed in the course of preliminary work.

The particulate systems under investigation were loaded into a cylindrical container $^3/_4$ in. in diameter and 6 in. in length. Loading was carried out by alternately adding the components in small increments to insure a random mixing initially. Samples taken at zero time showed standard deviations not significantly different from zero, indicating random mixing initially. The spheres contained in the cylinder were then subjected to a vertical sine wave motion at a frequency of 1025 c.p.m. and an amplitude of 0.100 in. for a predetermined time.

Vertical agitation was used since it was found to minimize segregation effects due to contact of the spheres with the cylinder walls. The shaking apparatus used was constructed to allow precise adjustment of both the rate and amplitude. Direct rate measurements were made with a Pioneer Photo-Tach model 12 tachometer to an accuracy of 5 c.p.m. In all cases the total weight of the systems was 171 Gm. which allowed sufficient space within the cylinder for expansion during shaking.

Sampling was accomplished by pushing the contents out of the cylinder with a plunger located in the bottom of the cylinder. This was done to divide the particles into six samples of approximately equal volume, allowing analysis of particle size distribution as a function of depth in the tube. Particle size analysis of the samples in these model systems was carried out by screening and weighing.

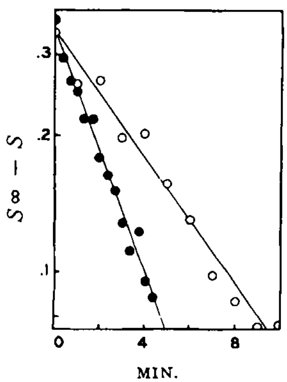

Fig. 2.—Semilog plot of equilibrium standard deviation minus standard deviation at time t *vs.* time of agitation, indicating apparent first-order approach to equilibrium. Solid points are at a 1:1 weight ratio of 8/32 *vs.* 3/32 in. steel balls. Open points are at a 1:1 weight ratio of 6/32 *vs.* 3/32 in. steel balls.

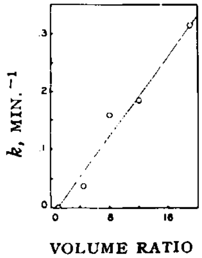

Fig. 3.—First-order rate constant k *vs.* the ratio of the particulate volumes of the spheres in the binary system. 3/32 in. steel balls were used in all runs at a 1:1 weight ratio with 5/32, 6/32, 7/32, and 8/32 in. steel balls, respectively.

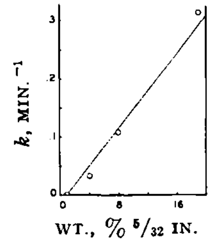

Fig. 4.—First-order rate constant k *vs.* the ratio of the particulate volumes of the spheres in the binary system. 8/32 in. steel balls were used in all runs at a 1:1 weight ratio with 6/32, 5/32, 4/32, and 3/32 in. steel balls, respectively.

TABLE I.—SEGREGATION RATE CONSTANTS IN BINARY SYSTEMS

Wt. Ratio in System	Size Ratio, 32nd in.	Particulate Volume Ratio	k, min.$^{-1}$
1:1	5:3	4.63	0.036 ± 0.003
1:1	6:3	8.00	0.161 ± 0.017
1:1	7:3	12.18	0.183 ± 0.025
1:1	8:3	18.96	0.314 ± 0.023
1:1	8:6	2.37	~0
1:1	8:5	4.10	0.033 ± 0.005
1:1	8:4	8.00	0.107 ± 0.007
1.2:1	7:3	12.18	0.136 ± 0.037
1.4:1	7:3	12.18	0.112 ± 0.016
1.6:1	7:3	12.18	0.103 ± 0.016

These data were used in calculating the standard deviation of the composition of the sample from the mean.

As previously mentioned, measurements of the standard deviation of particle size distributions made in this way are dependent on the size of the samples relative to the size of the particles. In the extremes, a sample consisting of the entire system will show no deviation from the mean composition, whereas samples containing one particle only will show complete segregation independent of the true state of the system. In the present work, samples of approximately one-sixth the weight of the total system were found to give a satisfactory estimate of the standard deviation.

Since the particulate system is disrupted by the sampling, it is necessary to carry out several experiments with each system. Repeated runs on a given system differing in duration of agitation are made so that the standard deviation is determined as a function of time of shaking.

RESULTS AND DISCUSSION

Time Dependence.—The results of two typical runs on systems containing equal weights of different size balls are shown in Fig. 1. When runs of extended duration are made it is found that segregation does not proceed to completion, which would correspond to a standard deviation of 0.500 in this case. Further, the same standard deviation is obtained from an initially unmixed system upon prolonged agitation as one which is initially randomly mixed, substantiating the existence of an equilibrium between mixing and unmixing. A typical system, 3/16 in. *versus* 3/32 in., was loaded with the large balls on top and the small balls at the bottom. Several standard deviations of this system after prolonged shaking were found not to differ significantly (using the "t" test) for those obtained from an initially randomly mixed system.

Figure 2 is a plot of log ($S_\infty - S$) *versus* time for the same runs as Fig. 1. S_∞ is the equilibrium standard deviation and S is the standard deviation at time t. The equilibrium standard deviation was taken as the average of three runs for times in excess of seven "half-lives." An initial estimate of half-life was obtained by treating the data by the method of Guggenheim (7) so that subsequent measurements of S_∞ could be made. It can be seen that the approach to equilibrium, of segregation in these systems, is an apparent first-order process.

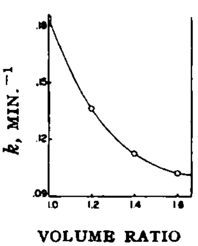

Fig. 5.—First-order rate constant k *vs.* the ratio by weight of 7/32 to 3/32 in. steel balls in the entire system.

TABLE II.—SEGREGATION RATE CONSTANTS IN TERNARY SYSTEMS

Wt. Ratio in System 3/32 in.:5/32 in.:7/32 in.	k (min.$^{-1}$) for Segregation of 7/32 in. Balls
50 : 0 :50	0.183 ± 0.025
37.5:12.5:50	0.108 ± 0.028
25 :25 :50	0.061 ± 0.013
12.5:37.5:50	0.034 ± 0.008
0 :50 :50	0.015 ± 0.004
45 :10 :45	0.115 ± 0.038
40.5:19 :40.5	0.066 ± 0.009
30.5:39 :30.5	0.066 ± 0.038
20.5:59 :20.5	0.061 ± 0.111

In these and subsequent determinations of segregation rate, rate constants were determined by the method of least squares from the kinetic data. Accuracy of the rate constants is expressed as a 95% confidence interval based on the student's "t" distribution. In these calculations, n-2 degrees of freedom were assumed, where n is the number of points on the curve. It was further assumed that the points were normally distributed, with constant variance about the regression line.

Particle Size Dependence.—Determinations of the effect of particle size on the segregation rate in binary systems indicate an apparent linear dependence on the volume ratio of the individual particles when the size of one component is held constant. Figure 3 represents determinations of rate constants of systems in which the size of the small spheres was held constant while that of the large spheres was varied. Values are for systems where 3/32 in. steel balls are mixed at a 1:1 weight ratio with 5/32, 3/16, 7/32, and 1/4 in. steel balls, respectively. Figure 4 shows the relationship of rate to size when the size of the smaller component is varied. The slopes of the lines in Figs. 3 and 4 are similar, indicating a consistent correlation of

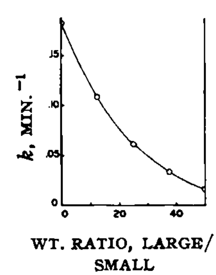

Fig. 6.—First-order rate constant k *vs.* weight per cent of 5/32 in. steel balls in a ternary system. The separation of the 7/32 in. steel balls was followed where the proportion of 7/32 in. steel balls was held at 50% by weight, and the proportion of 5/32 to 3/32 in. steel balls was varied within the balance of the system.

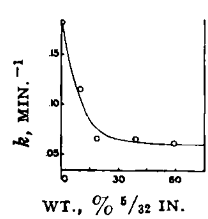

Fig. 7.—First-order rate constant k *vs.* weight per cent of 5/32 in. steel balls in a ternary system composed of a 1:1 weight ratio of 7/32 and 3/32 in. steel balls. Varying amounts of intermediate 5/32 in. steel balls were added, and segregation of the 7/32 in. steel balls was followed.

segregation rate *versus* particulate volume ratio. Values for 1/4 in. steel balls mixed at a 1:1 weight ratio with 3/16, 5/32, 1/8, and 3/32 in. steel balls, respectively, are given. These results, summarized in Table I, suggest that segregation effects may in part be due to competition by the particles for void space created during agitation. In this case, small particles would be favored and would tend to displace those which are larger, at the time of upward acceleration in each shaking cycle.

From lines 2 and 7 of Table I, a reduction in segregation rate with an increase in absolute particle size is apparent in systems where the particles have the same volume ratio. This effect may be because a greater percentage of the total number of particles contact the cylinder walls in systems of larger particles.

Weight Fraction Dependence.—Results shown in Fig. 5 illustrate the effect of variations in the relative quantities of the components in a binary system. Determinations were made in which the relative quantities of 7/32 and 3/32 in. steel balls were varied while maintaining a total weight of 171 Gm. The resulting rate constants, presented in Table I, have been plotted against the proportion of large to small spheres. It is interesting that the rate of segregation decreases with a decreasing proportion of small particles throughout the range studied. In addition, it was found that in systems where the particle size difference was small, this effect was much less.

Effect of Third Component.—In these studies the effect of intermediate size particles on segregation rate was investigated, and data are given in Table II. Figure 6 shows the results of experiments in which the system (171 Gm. total) is made up of 50% by weight of 7/32 in. spheres, and the remaining 50% consists of various ratios of 5/32 and 3/32 in. spheres. The rate of segregation of the 7/32 in. spheres has been plotted and is not a linear function of the composition of the remainder of the system. These data, when plotted as a function of the ratio of the particulate volume of 7/32 in. spheres to the weight average particulate volume of the mixture of 5/32 and 3/32 in. spheres, deviated somewhat from results such as those shown in Figs. 3 and 4. This can be expected, since the two small sized particles separate from each other as well as from the large particles.

The effect of the introduction of 5/32 in. intermediate particles to a 1:1 mixture by weight of 7/32 and 3/32 in. on the segregation rate of the 4/32 in. balls was also investigated. In this work, as before, the total weight of steel balls was held at 171 Gm. Results, shown in Fig. 7, indicate a marked reduction in unmixing tendencies with a relatively low proportion of 5/32 in. balls. Increasing this beyond a 33% mixture, in this case, resulted in little further change.

SUMMARY

It would appear, as in many preliminary studies of this type, that many more questions have been raised than answered. Several conclusions may be drawn from these studies:

The standard deviation of a system from its mean composition, as used previously, serves as a useful index to the state of mixedness of particulate systems.

Segregation of binary mixtures of spheres measured by the standard deviation from the mean composition follows apparent first-order approach to equilibrium for over two half-lives.

Segregation approaches a true equilibrium since both mixed and unmixed systems reach the same state after prolonged shaking.

The rate of segregation of particles in a binary system is apparently in direct proportion to the ratio of the particulate volumes of the spheres.

The overall weight ratio of the components in a binary system markedly affects the rate of segregation.

The presence of particles of intermediate size greatly reduces the rate of segregation in the system.

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