Tr. J. of Physics
23 (1999) , 97 – 104.

Assessment of the Degree of Mix of Powder Mixtures

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Received ...

Abstract

The older methods for the determination of the degree of a random mix was solely based on the calculation of a simple standard deviation. Physical characteristics like, density, average particle weight and size of each component was not considered. Therefore, the evaluation, when the state of a random mix is reached, was somewhat superficial. Poole, Taylor, and Wall [1] have derived equations, where the physical characteristics of the components were taken into consideration. By this means, it is possible to calculate, in advance, the theoretical coefficient of variation and the corresponding confidence limits. One can then experimentally follow under which conditions this state can be achieved.

1. Definition of Mixing

Mixing is the treatment of 2 or more components in such a way, that the individual particles of the different components in the mixture are evenly distributed and lie adjacent to each other within the highest possible probability.

2. Degree of Mixing

Starting from the initial situation, 2 different aims can be defined:
- perfect mixture (not achievable)
- random mixture (achievable).

¿From a pharmaceutical stand point, a mixture can be accepted to be homogeneous, if the state of a “random mix” is achieved.

3. Under Which Conditions can a Homogenous Mixture be Achieved?

- There must be enough space present, enabling free movement of the particles (filling level of the mixing apparatus).
- The energy input must move lateral to gravitation, enabling a shear of particles (type of mixer).
- The energy pumped into the system must be enough to overcome “adhesion” and “cohesion” between particles (speed of mixing and mixer type).

- The duration of the energy input must be long enough, enabling a random mixture, but should not exceed a critical mass which could cause segregation (duration of mixing).

4. The Goodness of a Mix Depends on the Following

- Construction of the mixing apparatus
- Duration of the mixing period
- Total amount of the powder
- Weight proportions of the different components to each other
- The physical properties of the individual components
- Mode of addition of the different components to the powder bed

5. Influence of Particle Properties on the Mixing Efficiency

1) Particle Size

Taking a binary mixture where p is one of the components, $(1-p)$ the second component and s the standard deviation;

$$s = \sqrt{\frac{p(1-p)}{n}}$$

This equation is valid for particles of same size, same particle form and density.

$p = 0.20; (1-p) = 0.80; n = 2000$

$$s = \sqrt{\frac{(0.2)(0.8)}{2000}} = 0.89\,\%$$

$p = 0.20; (1-p) = 0.80; n = 8000$

$$s = \sqrt{\frac{(0.2)(0.8)}{8000}} = 0.44\,\%$$

2) Flow Properties

A too good flow (with the least possible friction, adhesion and cohesion) in the presence of heterogeneous particle sizes or densities may sometimes lead to segregation even with the slightest movement (transport etc.). Therefore an optimal degree of flow must be tailored individually for a given powder mixture (with the help of angle of repose and/or flow time assessment).

3) Density and Particle Form

- Significant density differences promote segregation, due to percolation of the heavier particles through the less heavier one(s).
- It is very difficult to mix small particles of high density with big particles of small density.
- The particle form and the surface geometry influence the mixing efficiency through flow properties.

6. Statistical Methos for the Assesment of the Mixing Efficiency

1) Method of Simple Standard Deviation

In this method, the criteria of evaluation are the standard deviation of the content of the component under question (e.g. active ingredient). During each sampling period, the standard deviation of the samples (approximately 10 samples per sampling period) will be calculated.

The mixture will be accepted to be homogeneous (random mix) when
- e.g. from 10 samples, 9 samples show a standard deviation of less than 5 % and only one, more than 10 % and when the mean does not deviate more than 5 % from the target value.

This method does not consider any properties, like
- density, particle size, particle form, which may easily lead to erroneous interpretations.

2) Method of Poole, Taylor, and Wall [1]

$$\sigma_{\mathrm{R}}\% = \frac{100}{x}\sqrt{\frac{x \cdot y/M}{y \cdot \overline{m}_x + x \cdot \overline{m}_y}}$$

$\sigma_{\mathrm{R}}\%$ = Relative standard deviation of the smaller component
y = Weight proportion of the larger component $(1 - x)$
x = Weight proportion of the smaller component
M = Total weight
$\overline{m}_x$ = Mean particle weight of the smaller component
$\overline{m}_y$ = Mean particle weight of the larger component
$\overline{d}_v$ = Diameter of a particle of mean weight $\overline{m}$.
ρ = True density
where $\overline{m} = \dfrac{\pi \cdot \rho \cdot \overline{d}_v^{\,2}}{6}$

3) Method of Johnson [2]

Starting from the approach of Poole et al. [1], Johnson [2] has derived 2 formulas for low dosed mixtures ;

a) For mixtures of 0 – 1 % dose

$$\sigma_{\mathrm{R}}\% = \sqrt{\frac{\pi \cdot \rho}{6 \cdot G} \cdot \overline{d}_v^{\,3}} \cdot 100$$

b) For mixtures of 1 – 10 % dose

$$\sigma_{\mathrm{R}}\% = \sqrt{\frac{\pi \cdot \rho}{6 \cdot G} \cdot \overline{d}_v^{\,3}} \cdot 100 \cdot y$$

$\sigma_{\mathrm{R}}\%$ = Relative standard deviation of the content of the active ingredient
G = Weight of the active ingredient per dose (scale of scrutiny)
d = Mean particle size of the active ingredient expressed as volume distribution

ρ = True density of the active ingredient
y = Weight proportion of the inactive ingredients
$\overline{d}_v = (\Sigma f \cdot d^3)^{1/3}$
where f = fraction with the particle size $\overline{d}_v$.

7. Numerical Example

The theoretical coefficient of variation for a mixture of chlorambucil, lactose, cornstarch and talcum is to be assessed. For this purpose the data in Table 1 is used, which shows the results of the sieve analysis of chlorambucil.

Table 1. Sieve Analysis Results of Chlorambucil

Sieve Aperture (mm)	Amount on Sieve (g)	Mean Sieve Aperture d(mm)	d^3	Fraction of Chloram. (f)	fd^3	Sum of Fraction on Sieve
0.315	0.40					0.0033
0.250	67.61	0.283	0.02267	0.56	0.0127	0.5667
		0.225	0.0114	0.38	0.0043	
0.200	45.50					0.9459
		0.180	0.0058	0.04	0.000233	
0.160	5.22					0.9894
		0.143	0.00292	0.006	0.000018	
0.125	0.69					0.9952
		0.108	0.00126	0.0032	0.00	
0.090	0.38					0.9984
		0.045	0.00009	0.001	0.00	
						0.9994
				$\Sigma f \cdot d^3 =$	**0.0173**	

It is assumed that 10 samples per sampling time is taken by means of a sample thief (Fig. 1), and the corresponding sampling plan is shown in Fig. 2.
Density of chlorambucil = 150 gcm^{-3}

MIXTURE

Chlorambucil	0.050 g (5%)
Lactose	0.830 g
Cornstarch	0.100 g
Talcum	0.020 g
TOTAL	1.000 g

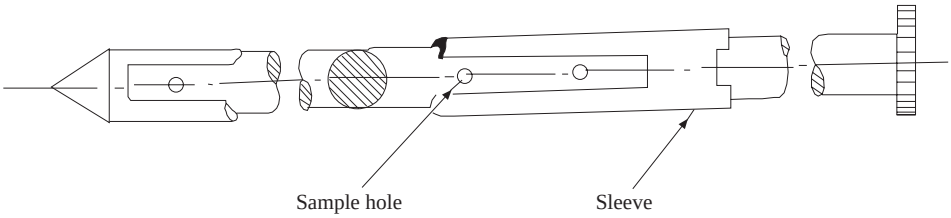

Figure 1. Sample Thief

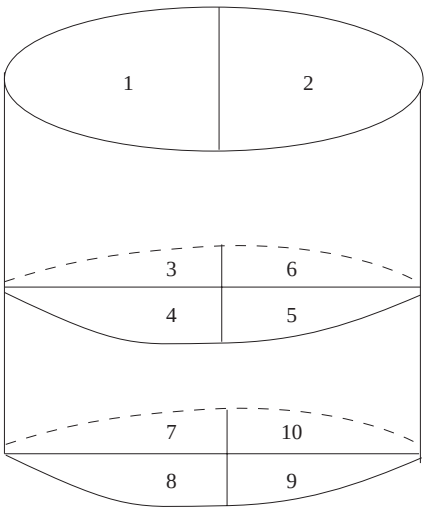

Figure 2. Sampling Plan

The THEORETICAL coefficient of variation for a random mix can be calculated as follows :

As seen from Table 1:

$\Sigma f \cdot d^3 = 0.0173$

$\left(\Sigma f \cdot d^3\right)^{1/2} = 0.1310$

$\overline{d}_v = \left(\Sigma f \cdot d^3\right)^{1/3} = 0.259\,\text{mm}$

$$\begin{aligned}\sigma_{\text{R}}\% &= \left(\frac{\pi \cdot \rho}{6G}\right)^{1/2} \cdot \left(\Sigma f \cdot d^3\right)^{1/2} \cdot 100 \cdot y \\ &= (100)(0.95)\left[\frac{(3.14)(0.0015)}{6 \cdot (0.005)}\right]^{1/2} (0.0173)^{1/2} \\ &= 1.57\end{aligned}$$

The calculated coefficient of variation comprises biases, of which the method of analysis is the most significant one. Therefore the total coefficient of variation can be calculated to be:

$c_{v(Total)} = \left[c_{VM}^2 + c_{VA}^2\right]^{1/2}$
c_{VM} = Coefficient of variation of the mixture
c_{AM} = Coefficient of variation of the analysis method

Calculation of the Coefficient of Variation of the Analysis Method

For this purpose, known concentrations can be calculated with the help calibration line (by using the slope from least squares analysis):

Weighed	Found (%)
0.20442	101.5
0.19758	102.4
0.19900	101.3

$\overline{x} = 101.7\,\%$
$s = 0.587$
$c_{VA} = s/\overline{x} \cdot 100 = 0.577\,\%$
$c_v(Total) = \left[(1.57)^2 + (0.577)^2\right]^{1/2} = 1.67\,\%$
and the 95 % confidence limits
$1.15\,\% \leq c_{v(Total)} \leq 3.04\,\%$

8. Calculation of Confidence Limits of a Variance

$$\frac{s^2(n-1)}{\chi^2_{(n-1)};\alpha/2} < \sigma < \frac{s^2(n-1)}{\chi^2_{(n-1)};1-\alpha/2}$$

lower limit upper limit

- For 95 % probability level ($\alpha = 0.05$)
- For 10 samples per sampling period

Lower limit
$n = 10$
$n - 1 = 9$
$\alpha/2 = 0.025$

Upper limit
$n = 10$
$n - 1 = 9$
$1 - \alpha/2 = 0.975$

Johnson [2] has followed the coefficient of variation of 1 % milled cyclopenthiazide as a function of mixing time (Figs. 3 and 4).

As shown by Figs. 3 and 4, after having calculated the theoretical coefficient of variation and the corresponding confidence limits, one can then follow the elapsed time by which the coefficient of variation of the sample content would lie within the confidence limits of the calculated theoretical coefficient of variation. By this means it is possible to decide when the state of a random mix is achieved. As Figs. 3 and 4 show, there is an optimal mixing time for a given mixture, after which further mixing can lead to

segregation.

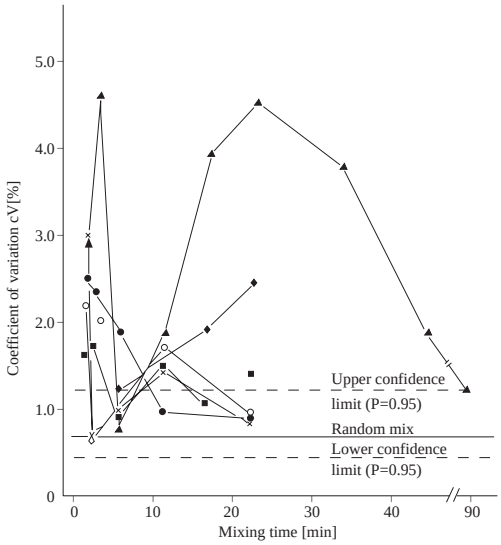

Figure 3. C_v results for 1 % mixtures of milled cyclopenthiazide, as a function of mixing time (From Ref. 2).

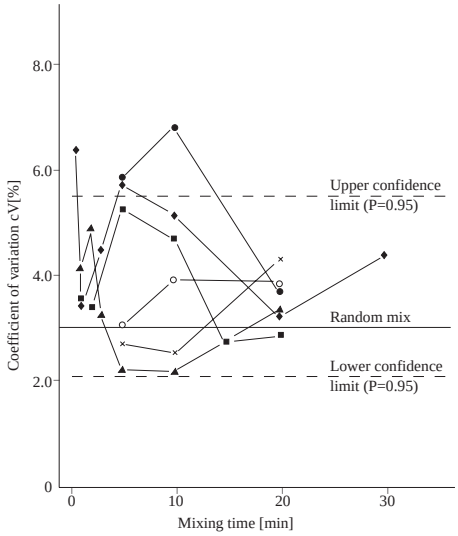

Figure 4. C_v results for 1 % mixtures of unmilled cyclopenthiazide, as a function of mixing time (From Ref. 2).

References

[1] R.K. Poole, F.R. Taylor, and P.G. Wall *Trans. Inst. Chem. Eng.* **42** (1964) T166.

[2] M.R.C. Johnson, *Pharm. Act. Helv.* **50** (1975) 61.