Evaluation of the Poisson Distribution for Estimating the Quality of Drug/Diluent Random Powder Mixtures. I. High Particle Size of the Drug Constituent

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Use of the Poisson distribution to estimate the quality of random mixtures was evaluated as a measure of the highest attainable degree of dose uniformity of tablets. Ingredient A was assumed to have a large particle size as compared to diluent B. In contrast to the more precise binomial distribution, for the simple Poisson approach no experiments are necessary to investigate the mean proportions of the apparent volume, a_v and b_v, which A and B assume within the powder samples in the die. The range of volume ratios was defined where the Poisson distribution is valid. Accepting an error of 5% of the random content variation of A per sample, a_v may amount to up to 0.1 (10%). In terms of the proportion by mass of A, a, this range is wider, and commonly of the order of 0.2 or higher. This approach was tested with tablets prepared from mixtures of coarse sucrose A and a fine Avicel/talc diluent B at A:B (m:m) ratios from 10:90 to 50:50. Even with the 30:70 tablets, the variations of the sucrose content were still in good agreement with the content variations of the random mixtures as estimated from the Poisson distribution. Estimates of the 50:50 ratio, however, deviated from the Poisson distribution.

KEY WORDS: powder mixing; random mixtures; highest degree of mixing; quality of random mixtures; Poisson distribution; dose uniformity.

INTRODUCTION

In 1943, Lacey (1) proposed the highest degree of mixing to equal the quality of the random mixture, a concept of broad validity to pharmaceutical powder mixtures. With directly compressed tablets, the random degree of homogeneity was obtained using both free-flowing and cohesive interactive ingredients (2,3). In contrast, the formation of ordered mixtures of higher degree of homogeneity has so far not been demonstrated clearly (4) and, from theory, is not expected to occur under actual mixing conditions (3,5). Hence the random mixing quality may be utilized as a measure of the highest degree of dose uniformity which can be attained with solid dosage forms under ideal mixing and processing conditions.

Recently (6) an equation for the quality of binary random mixtures has been derived from the binomial distribution. In contrast to the approaches of Stange (7) and of Poole *et al.* (8), which assume powder samples of constant mass, this equation provides the powder mixture to be divided into samples of constant bulk volume, as it conforms to tabletting and capsule filling. Experimentally, this equation was verified with constituents showing significant differences in particle size and bulk density (6), as is frequently the case with pharmaceutical systems.

As a limitation to simple use, however, this novel approach applies the ratio by volume which the constituents adopt in the mixture. In practice, only the ratio by mass is known a priori. Methods for estimating the volume ratio have been developed but imply additional experimental work (9).

Problems of a high dose uniformity arise predominantly with low dosage forms, where, in general, the active ingredient amounts to a small proportion only. Then the Poisson distribution may be utilized to estimate the random content variation of the active ingredient per sample. Johnson (10) has derived an adequate equation, which was modified by Egermann (11) and successfully applied to drug/diluent powder mixtures (3,10). The Poisson distribution needs no estimate of the volume ratio and, thus, provides a more simple approach to the theoretically highest dose uniformity.

So far, however, the validity range of the Poisson distribution has not been fully evaluated. Johnson (10) proposed the proportion of the active ingredient not to exceed 1% by mass, whereas Egermann *et al.* (3) suggested a limit of 10%. According to the theory developed recently (6,9), it is not the ratio by mass, but rather by bulk volume, that is the defining parameter. Moreover, the applications of the Poisson distribution may be different, dependent on whether the active ingredient shows a particle size larger or smaller than the diluent component.

In this communication, the validity range of the Poisson distribution is examined with mixtures where the ingredient is large in particle size as compared to the diluent. The binomial equation is also considered to estimate the precision of the Poisson approach.

THEORY

Binomial Distribution

The novel binomial equation (6) shows the general form

$$\sigma_{RB} = \sqrt{\frac{a_v \cdot b_v \cdot \bar{v}_a}{V}} \qquad (1)$$

σ_{RB} = standard deviation of the sample composition of the random mixture, as a proportion of the sample volume V

a_v = mean proportion by apparent volume of the coarse constituent A per sample

b_v = $1 - a_v$ = mean proportion by apparent volume of the fine constituent B per sample

$\bar{v}_a$ = representative mean particle volume of A

V = constant bulk volume of the samples (according to the die volume in tabletting)

In terms of the coefficient of variation, as a percentage of the mean a_v of A per sample, Eq. (1) becomes

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$$C_{RaB} = 100 \sqrt{\frac{b_v \cdot \bar{v}_a}{a_v \cdot V}} \quad (2)$$

The quantity of this percentage C_{RaB} is independent of whether the mean is expressed in dimensions of volume or of mass.

The representative mean particle volume $\bar{v}$ conforms to the volume/weighted-volume/number mean diameter $\bar{d}_v$,

$$\bar{v} = \frac{\bar{d}_{v^3} \cdot \pi \cdot F}{6} \quad (3)$$

F is the volume shape factor (spheres: $F = 1$).

Assuming a cylindrical tablet die and a plane surface of the lower punch, the die volume (sample volume) V is derived from the diameter D and the depth h of the die:

$$V = \frac{D^2 \cdot \pi \cdot h}{4} \quad (4)$$

a_v and b_v (equal $1 - a_v$) of Eq. (2) may be estimated from the mass proportions a and b of constituents A and B.

$$a_v = \frac{a}{a + b \cdot Q_w} \quad (5)$$

Q_w is the quotient of the "working densities" ρ_{wa} and ρ_{wb}, which are the apparent bulk densities that constituents A and B of the mixture assume in the die:

$$Q_w = \frac{\rho_{wa}}{\rho_{wb}} \quad (6)$$

To derive Q_w and the working densities, respectively, two approaches have been described, which differ in their validity ranges (9). The first was established with intermediate ratios a_v:b_v between the percolation thresholds P_{ca} and P_{cb}. In this range, both A and B form a coherent structure ("infinite clusters") in the system. Then the working densities ρ_{wa} and ρ_{wb} are significantly smaller than the particle densities ρ_a and ρ_b. In practice, this may be the case if the portions of both a_v and b_v amount to at least 0.3 (9).

Q_w may be estimated from the quotients Q_{pour} and Q_{tap} of the poured and the tapped densities by linear extrapolation to the working density ρ_w of the mixture in the die:

$$Q_w = \frac{(\rho_{tap} - \rho_w)(Q_{pour} - Q_{tap})}{\rho_{tap} - \rho_{pour}} + Q_{tap} \quad (7)$$

ρ_{pour} and ρ_{tap} are the theoretical poured and tapped densities of the mixtures, as calculated additively from the poured and the tapped densities of the individual constituents A and B. These estimated values of the densities of the mixtures are sufficiently adequate and reliable as previously demonstrated (9).

ρ_w may be determined experimentally from the mean sample (tablet) mass $\bar{M}$ and the die volume V,

$$\rho_w = \frac{\bar{M}}{V} \quad (8)$$

ρ_{wa} and ρ_{wb} of Eq. (6) are related to ρ_w according to

$$\frac{a}{\rho_{wa}} + \frac{b}{\rho_{wb}} = \frac{1}{\rho_w} \quad (9)$$

Applying Eq. (9) to Eq. (6), the individual values ρ_{wa} and ρ_{wb} are also derived.

The second approach was found valid with small portions a_v below 0.1. Then the particles A may be dispersed individually within the coherent matrix of B, and ρ_{wa} assumes the particle density ρ_a of A. With ρ_a being known, ρ_{wb} may be calculated as

$$\rho_{wb} = \frac{b \cdot \rho_a \cdot \rho_w}{\rho_a - a \cdot \rho_w} \quad (10)$$

To facilitate comparison of Eq. (2) to the Poisson distribution, the apparent volume V_a of A per sample of total volume V is introduced:

$$V_a = V \cdot a_v \quad (11)$$

Then Eq. (2) of the "random content variation" C_{RaB} of A per sample appears as

$$C_{RaB} = 100 \sqrt{\frac{\bar{v}_a \cdot b_v}{V_a}} \quad (12)$$

Poisson Distribution

Johnson's equation (10) as extended by Egermann (11) applies the parameters by mass of ingredient A:

$$C_{RaP} = 100 \sqrt{\frac{\bar{m}_a}{M_a}} \quad (13)$$

C_{RaP} is the coefficient of variation of A as a percentage of the mean content by mass M_a of A per sample. $\bar{m}_a$ is the representative mean particle mass of A and is related to $\bar{v}_a$ by

$$\bar{m}_a = \bar{v}_a \cdot \rho_a \quad (14)$$

The mean mass M_a of A occupies a corresponding apparent mean volume V_a in the samples,

$$M_a = V_a \cdot \rho_{wa} \quad (15)$$

From the mixing theory presented recently (6), the quantities of A by volume rather than by mass of Eq. (13) are representative of the random variation of the content A per sample. Substituting Eqs. (14) and (15) into Eq. (13), a more correct formula is derived, where the random content variation is defined in terms of the relevant volume parameters

$$C_{RaP(v)} = 100 \sqrt{\frac{\bar{v}_a \cdot \rho_a}{V_a \cdot \rho_{wa}}} \quad (16)$$

With small proportions a_v, however, the working density ρ_{wa} approaches the particle density ρ_a of A,

$$\rho_{wa} = \rho_a \quad (17)$$

If the condition of Eq. (17) is met, Eq. (16) takes the following form, which is equivalent to Eq. (13):

$$C_{RaP(v)} = C_{RaP} = 100 \sqrt{\frac{\bar{v}_a}{V_a}} \quad (18)$$

In practice, M_a of Eq. (13), in contrast to V_a, is known a priori. Accordingly, the more simple approach of Eq. (13) may be appropriate as long as Eq. (17) is satisfied. From the limited evidence available so far, this may be anticipated with $a_v \leq 0.1$ (9).

Error of the Poisson Distribution

From Eqs. (12) and (18), the following relation between the binomial and the Poisson distribution is obtained:

$$C_{RaB} = C_{RaP}\sqrt{b_v} \tag{19}$$

Equation (19) shows the Poisson distribution of Eq. (13) to yield higher values of C_{Ra} than the more precise binomial approach. The quantity of this error depends on the ratio b_v and equals

$$C_{RaP(error)} = \frac{1}{\sqrt{b_v}} \tag{20}$$

Arbitrarily, an error of 5% in the value of C_{RaP} may be acceptable in practice; since even the statistical error inherent to the spot sample assay of the actual batch dose uniformity is larger. Assuming a comparatively large sample size of 30 units, as used at the second step of the USP-Content Uniformity Test, and a normal distribution, the 95% confidence limits are of the order of 25% of the coefficients of variation found. In comparison, an error of 5% in the estimate of the theoretically lowest coefficient of variation appears minor.

Equation (20) provides the error of C_{RaP} not to exceed 5% with $b_v \geq 0.9$ and $a_v \leq 0.1$. This ratio just conforms with the limit of a_v, up to which the particles A may be assumed to be dispersed individually and to satisfy Eq. (17) with ρ_{wa} equal ρ_a (9).

The value of ρ_a of a coarse ingredient may be assumed to be significantly higher than ρ_{wb} of the diluents. Organic drug substances frequently show a true density ρ_a near 1.5 g/ml. The density ρ_{wb} of common tabletting vehicles such as starches and lactose powders assumes values between the poured and the tapped density and, thus, is of the order of 0.7 g/ml. With ρ_a being 2.2 times ρ_{wb} and $a_v = 0.1$, Eq. (5) yields the proportion by mass, a, as 0.2.

These theoretical considerations suggest that the Poisson approach, in dimensions of mass (Eq. 13), may be applied with ratios of a coarse ingredient A up to almost 20% by mass. Within this range, experimental evaluation of a_v to allow the use of the binomial Eq. (2) will be necessary in exceptional cases only.

MATERIALS AND METHODS

Sucrose, $\bar{d}_v = 504$ μm ($\bar{v}_a = 0.067$ mm^3) was used as the coarse ingredient A with the true density ρ_a of 1.59 g/ml. The fines B were composed of an Avicel pH 101/talc mixture (80:20 m:m) with $\bar{d}_v$ approximately 60 μm. Three A:B (m:m) ratios, 10:90, 30:70, and 50:50, were studied after mixing for 30 min on a Turbula T 2C shaking mixer. Batch size varied from 320 to 600 g in order to keep the filling level of the 2-liter vessel approximately constant. The mixtures were directly compressed to 200-mg tablets (9-mm diameter) on a single-punch machine EKO at 45 tablets/min using a spin feeder. Two independent batches were produced at each of the ratios. Random spot samples of 30 tablets each were assayed spectrophotometrically at 190 nm under a nitrogen atmosphere at 25 ± 0.1°C for individual sucrose content.

Full details have been given elsewhere (6).

RESULTS AND DISCUSSION

Table I shows the relevant parameters by mass, volume, and density of constituents A and B. At A:B ratios of 10:90 and 30:70, method 2 under Theory section has previously (9) been found valid, which assumes that the working density ρ_{wa} of sucrose A is equal to its true density ρ_a of 1.59 g/ml. The low working density ρ_{wb} of the Avicel/talc vehicle B, 0.34 g/ml, and the high density quotient Q_w, 4.7, results in small a_v values. Even at the 30:70 ratio, a_v was only 0.08, and still within the applicability of the Poisson distribution. However, method 2 was no longer valid for the 50:50 mixture, while method 1 did apply, yielding an a_v value of 0.33.

According to the small proportions a_v at the lower ratios, Eqs. (13) and (16) of the Poisson distribution produced random content variations C_{RaP} of 7.3% (10:90) and 4.2% (30:70), which were similar to the values C_{RaB} of 7.2 and 4.0% from the binomial distribution of Eq. (2). As expected from theory, at the 50:50 ratio, the C_{RaP} of 3.3% was significantly higher than the C_{RaB} of 2% (Table II).

The experimental coefficients of variation of the sucrose content, C_a, conformed reasonably well with theory and showed good reproducibility with the two tablet batches per ratio assayed. The C_a of 9.7 and 10.1% found with the 10:90 tablets was slightly higher than calculated for the random mixtures and was within the magnitude of the upper confidence limit of the random values C_{Ra}. Besides some nonuniformity of die filling (12), this deviation may be attributed to minor segregation of the sucrose particles, which presumably occurred during processing of the mixtures as a consequence of the loose packing structure of the Avicel matrix.

On increasing the ratio, segregation was further minimized. With the 30:70 tablets, the content variations C_a of 4.6 and 4.7% were well within the confidence intervals of the

Table I. Parameters by Mass, Density, and Volume of the Mixtures of Sucrose (A) and Avicel/Talc (B)

A:B (m:m)	a	b	ρ_w (g/ml)	ρ_{wa} (g/ml)	ρ_{wb} (g/ml)	Q_w	a_v	b_v	V(ml)	V_a (ml)
10:90	0.1	0.9	0.38	1.59	0.35	4.6	0.02	0.98	0.54	0.011
30:70	0.3	0.7	0.44	1.59	0.34	4.7	0.08	0.92	0.45	0.035
50:50	0.5	0.5	0.57	0.86	0.43	2.0	0.33	0.67	0.35	0.12

Table II. Variations of the Sucrose Content of the 200-mg Tablets Calculated and Found

A:B (m:m)	Calculated C_{RaB} % (interval)[a]	Calculated C_{RaP} % (interval)	Found C_a %	Batch
10:90	7.2	7.3	9.7	K4
	(5.6–9.7)	(5.7–9.9)	10.1	K10
30:70	4.0	4.2	4.7	K6
	(3.2–5.5)	(3.3–5.7)	4.6	K12
50:50	2.0	3.3	2.1	F7
	(1.5–2.7)	(2.6–4.4)	2.2	F8

[a] Confidence interval ($P = 0.95$, $n = 30$).

C_{Ra} values, as conforming to tablets of random mixtures. At the 50:50 ratio, the C_a of 2.2 and 2.1% showed excellent agreement with the C_{RaB} of 2%. On the other hand, the C_a was significantly below the C_{RaP} of 3.3% and further confirmed that the Poisson approach no longer applied to this high ratio.

These results confirm that the validity range of the Poisson distribution to estimate the highest attainable dose uniformity of tablets is significantly broader than suggested previously. The defining parameter is the ratio by apparent volume of constituents A and B in the powder samples. With a_v of the coarse ingredient A up to 0.1, corresponding to b_v 0.9, the quantity of the random content variation of A per sample does not exceed an error of 5%.

Within this range of a_v, the working density ρ_{wa} of A approaches the true density ρ_a, which, in general, is substantially higher than the bulk density ρ_{wb} of the fine diluent B. In this case the proportion of A by mass is larger than that by volume. With the sucrose/Avicel system examined, the Poisson approach still applied at 30% of A by mass. This upper limit was a consequence of the exceptionally low value ρ_{wb}, which yielded a high density quotient Q_w of 4.7. However, with the majority of the powder systems common in pharmaceutical practice, Q_w may be assumed to be two or larger. This condition suggests a broad validity of the simple Poisson approach of Eq. (13) with proportions of a coarse ingredient A up to 20% by mass of the total mixture.

NOMENCLATURE

a (subscript)	Parameter of the coarse constituent A
a	Mean proportion by mass of A per sample
A	Coarse constituent of a high working density
a_v	Mean proportion by apparent volume of A per sample
B (subscript)	Parameter derived from the binomial distribution
b (subscript)	Parameter of the fine constituent B
$b = 1 - a$	Mean proportion by mass of B per sample
B	Fine constituent of a low working density
$b_v = 1 - a_v$	Mean proportion by apparent volume of B per sample
C	Coefficient of variation of the mean content of a constituent per sample, found on tablet assay
C_R	Coefficient of variation of the mean content of a constituent per sample (tablet) of the random mixture ("random content variation")
$\bar{d}_v$	Volume-weighted/volume-number mean diameter
D	Diameter of the die
F	Volume shape factor
h	Depth of the die
$\bar{m}$	Representative mean particle mass
$\bar{M}$	Mean sample mass (tablet weight)
M_a	Mean mass of a constituent per sample
p (subscript)	Parameter derived from the Poisson distribution
P_c	Percolation threshold of a constituent
Q_w	Quotient of the working densities ρ_w of A and B
Q_{pour}	Quotient of the poured densities ρ_{pour} of A and B
Q_{tap}	Quotient of the tapped densities ρ_{tap} of A and B
ρ	Density of the particles
ρ_{pour}	Poured density
ρ_{tap}	Tapped density
ρ_w	Working density (bulk density in the die); working density of the mixture of A and B
σ_{RB}	Standard deviation of the sample composition of the random mixture, in terms of the proportion of the sample volume V
v (subscript)	Parameter in dimensions of volume
$\bar{v}$	Representative mean particle volume of a constituent
V	Constant bulk volume of the samples (according to the die volume in tabletting)
V_a	Apparent mean volume of A per sample

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