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Mass variation of powder samples of constant volume produced from binary random mixtures. I. Derivation of the equation

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Summary

Direct compression of drug/diluent powder mixtures may produce tablet mass variation, if the constituents are different in their bulk density in the die (working density). An equation of the mass variation of powder samples of constant bulk volume drawn from binary random mixtures is derived. This equation provides a measure of the tablet mass variation, which results from the random variation of the sample composition in the die. The validity of this equation was verified by direct compression of mixtures composed of a coarse constituent of high working density (sucrose) and a fine constituent of low working density (Avicel PH 101 and Avicel PH 101/talc, respectively). The mass variations found with the tablets were in good agreement with those predicted from the equation.

Introduction

In tabletting, granulations or powder mixtures are divided into samples of constant volume, according to the filling capacity of the die. Variations in tablet mass generally are attributed to non-uniformity of die filling, e.g. as a consequence of poor flowability of the powders. Another source of tablet mass variations, which may be of particular importance in direct compression, is variation in sample composition. With binary powder mixtures (drug/diluent), samples of constant volume may yield tablets of constant mass only, if the bulk density of the constituents in the die ('working density') is identical. In the case of differences in the working density, as is customary with constituents differing in particle size, the sample mass is not constant but increases with increasing content of the constituent of higher working density.

In this paper, an equation is derived for the mass variation produced by samples of constant volume of binary random mixtures. Since the quality of the random mixture conforms to the

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highest attainable degree of mixing (Egermann and Frank, 1991), this equation estimates the smallest tablet mass variation, that may be produced with uniform die filling and in the absence of segregation.

Theory

From the binomial distribution, the quality of binary random mixtures, where the samples are drawn by constant volume, has recently been derived (Egermann and Frank, 1991) as:

$$\sigma_R = \sqrt{\frac{a_v b_v \bar{v}_a}{V}} \tag{1}$$

where σ_R is the standard deviation of the sample composition of the random mixture in terms of the volume proportion of the apparent sample volume V, a_v denotes the mean proportion by apparent volume of the coarse constituent A per sample, b_v $(= 1 - a_v)$ is the mean proportion by apparent volume of the fine constituent B per sample, $\bar{v}_a$ is the representative mean particle volume of A, and V represents constant sample volume (die volume).

Eqn 1 shows the extent of random variation of sample composition to be dependent on the particle volume $\bar{v}_a$ of the coarse constituent A only. In contrast to previous approaches of Stange (1954), and of Poole et al. (1964), it applies to mixtures where the constituents differ in particle size and in working density.

In pharmaceutical practice, the coefficient of variation, as a percentage of the mean of the active ingredient per sample (tablet, capsule), is of interest. With the coarse constituent A:

$$C_{Ra} = 100\sqrt{\frac{b_v \bar{v}_a}{a_v V}} \tag{2a}$$

With the fine constituent B:

$$C_{Rb} = 100\sqrt{\frac{a_v \bar{v}_a}{b_v V}} \tag{2b}$$

C_{Ra} and C_{Rb} are the coefficients of variation as a percentage of the mean of A and B, respectively, per sample of constant volume of the random mixture ('random content variations' of A and B).

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

$$\bar{v} = \frac{\bar{d}_v^3 \pi F}{6} \tag{3}$$

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

As a rule, the coarse constituent A may be assumed to feature a higher working density than the fines B within the range of validity of Eqn 1 (Egermann et al., 1991). Then the individual mass of samples of constant volume is directly related to their content of A. The quantity to which the random content variation C_{Ra} of A does produce a mass variation of the samples is dependent on the difference between the working densities ρ_{wa} and ρ_{wb}, in terms of the dimensionless 'density coefficient' k_{wa}:

$$k_{wa} = \frac{\rho_{wa} - \rho_{wb}}{\rho_{wa}} \tag{4a}$$

If the fines B show the higher working density, the density coefficient k_{wb} is:

$$k_{wb} = \frac{\rho_{wb} - \rho_{wa}}{\rho_{wb}} \tag{4b}$$

The random content variation C_{Ra} of Eqn 2a is expressed as the percentage of the mean of constituent A per sample. The percentage is smaller if related to the tablet mass M, and amounts only to a times C_{Ra}, where a is the mean proportion by mass of A per sample. Accordingly, the corresponding tablet mass variation may be derived from C_{Ra} as:

$$C_{Rt} = k_{wa} a C_{Ra} \tag{5a}$$

where C_{Rt} is the coefficient of variation of the mass of samples of constant bulk volume V drawn from the random mixture, as a percentage of the

mean sample (tablet) mass M ('composition-dependent random variation of tablet mass').

With Eqn 2a for C_{Ra}, Eqn 5a takes the final form:

$$C_{Rt} = 100k_{wa}a\sqrt{\frac{b_v\bar{v}_a}{a_vV}} \tag{6a}$$

Alternatively, with the fines B being of higher working density, C_{Rt} is derived from Eqns 2b and 4b as:

$$C_{Rt} = 100k_{wb}b\sqrt{\frac{a_v\bar{v}_a}{b_vV}} \tag{6b}$$

C_{Rt} is a measure of the highest uniformity of tablet mass that may be attained under ideal processing conditions only. In practice, additional tablet mass variations may result from constituent segregation (incomplete degree of mixing respectively) and from non-uniformity of the die filling.

The volume proportions a_v and b_v may be estimated from the mass proportions a and b (equal to $1-a$) of A and B:

$$a_v = \frac{a}{a + bQ_w} \tag{7}$$

Q_w is the quotient of the working densities ρ_{wa} and ρ_{wb}:

$$Q_w = \frac{\rho_{wa}}{\rho_{wb}} \tag{8}$$

ρ_{wa} and ρ_{wb} are related to ρ_W, the working density of the mixture of A and B in the die, according to:

$$\frac{a}{\rho_{wa}} + \frac{b}{\rho_{wb}} = \frac{1}{\rho_w} \tag{9}$$

From Eqn 9, ρ_{wb} is given by:

$$\rho_{wb} = \frac{b\rho_{wa}\rho_w}{\rho_{wa} - a\rho_w} \tag{10}$$

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

$$\rho_w = \frac{\bar{M}}{V} \tag{11}$$

To derive ρ_{wb} of Eqn 10, two methods have recently been evaluated (Egermann et al., 1991), which differ in their range of application. With quantities of a_v lower than 0.1, as used in the present study, method 2 was found valid, where ρ_{wa} is supposed to equal the particle density ρ_a of A. Then ρ_{wb} may be estimated from Eqn 10, and in turn, Q_w of Eqn 7 is available from Eqn 8.

Materials and Methods

The experimental conditions essentially conformed to earlier work (Egermann and Frank, 1991) and have been found to produce random mixtures with the constituents under considera-

TABLE 1

Variations of tablet mass calculated and found with 50 mg tablets (constituents: sucrose (A), Avicel PH 101 (B))

Ratio A : B (m : m)	ρ_w (g/ml)	ρ_{wa} (g/ml)	ρ_{wb} (g/ml)	C_{Rt}(%) (interval)	C_t(%)	Batch
10 : 90	0.32	1.59	0.29	1.2 (0.9–1.6)	1.3 1.5	K14a K14b
20 : 80	0.35	1.59	0.29	1.6 (1.3–2.2)	1.7 1.9	K15a K15b
30 : 70	0.41	1.59	0.31	2.0 (1.5–2.7)	2.2 2.4	K16a K16b

Interval = confidence interval ($P = 0.95$, $n = 30$).

TABLE 2

Variations of tablet mass calculated and found with 50 mg tablets (constituents: sucrose (A), Avicel PH 101 / talc (80 : 20 (B))

Ratio A : B (m : m)	ρ_w (g/ml)	ρ_{wa} (g/ml)	ρ_{wb} (g/ml)	C_{Rt}(%) (interval)	C_t(%)	Batch
10 : 90	0.39	1.59	0.36	1.1 (0.9–1.5)	1.4 1.5	K17a K17b
20 : 80	0.44	1.59	0.36	1.5 (1.2–2.1)	1.8 1.8	K18a K18b
30 : 70	0.47	1.59	0.37	1.9 (1.5–2.5)	2.3 2.6	K19a K19b

Interval = confidence interval ($P = 0.95$, $n = 30$).

tion. Sucrose, $\bar{d}_v$ 504 μm ($\bar{v}_a$ 0.067 mm^3), was used as the coarse constituent A of high working density ρ_{wa}, which was assumed to equal to the true density ρ_a of 1.59 g/ml. Avicel PH 101 alone, and an Avicel PH 101/talc (80 : 20) mixture with $\bar{d}_v$ approx. 60 μm were the fine constituents B of low ρ_{wb}. Three $m : m$ ratios A : B of 10 : 90, 20 : 80, and 30 : 70 were studied with the batch size varying from 320 to 500 g, in order to keep the filling level of the 2 l mixing vessel approximately constant. Mixing for 30 min was accomplished in a Turbula T 2 C shaking mixer. Direct compression to tablets of 50 mg (5 mm diameter) was performed on an EKO single-punch machine at 45 tablets/min using a spin feeder. Two spot samples of 30 tablets each were drawn randomly from each batch and weighed individually.

Results

Tablets with Avicel PH 101 as constituent B (Table 1)

The working density ρ_w of the 10 : 90 mixture was found to be 0.32 g/ml, and increased with increasing sucrose ratio up to 0.41 g/ml (30 : 70), according to the high working density ρ_{wa} of sucrose A equal to 1.59 g/ml. ρ_{wb} of the B-portion, however, remained almost constant (0.29–0.31 g/ml) with the mixing ratios studied.

The values of the random tablet mass variation C_{Rt} of Eqn 6a were derived as 1.2% (10 : 90), 1.6% (20 : 80), and 2.0% (30 : 70). On comparison with the experimental results, one has to consider that C_{Rt} is representative of the random mixing error only. It does not comprise the additional mass variations that may be due to segregation of the constituents and to non-uniformity of the die filling. Nevertheless, the tablet mass variations C_t found were in satisfactory agreement with the values C_{Rt}. Just like C_{Rt}, they increased with increasing sucrose ratio from 1.3% (1.5% on repeated sampling) to 1.7 (1.9%) and 2.2 (2.4%). With no sample, C_t was found to be outside the 95% confidence interval of C_{Rt}.

Tablets with Avicel PH 101 / talc as constituent B (Table 2)

Using the Avicel/talc mixture, results similar to those of the talc-free tablets were found. Indeed, the working density ρ_{wb} of 0.36–0.37 g/ml was slightly higher than of Avicel alone. This difference, however, was still of minor importance compared to the quantities of the random mass variations C_{Rt}, which were almost identical to those of the talc-free tablets. The experimental mass variations C_t were found to be slightly above the corresponding values of C_{Rt}, but still within the confidence intervals of C_{Rt} with five of the six samples examined. In accordance with C_{Rt}, C_t again increased with increasing sucrose content of the tablets from 1.4 (1.5%) to 1.8 (1.8%) and 2.3 (2.6%).

Discussion

The present results strongly support the validity of Eqn 6 for defining the variation of tablet mass that is produced by the random variation of the

sample composition in the die. The effect of the sucrose content on the experimental mass variations C_t conformed well to that expected from Eqn 6. Indeed, the quantities of C_t were found to be slightly higher than the corresponding values C_{Rt}. This, however, may be anticipated from the additional mass errors inherent in C_t which, in practice, cannot fully be avoided. A C_t value significantly smaller than the theoretical minimum C_{Rt} has never been found.

The satisfactory agreement between C_{Rt} and C_t further indicates that the segregation and the non-uniformity of die filling were minimized with the mixing and tabletting conditions applied. Obviously, these additional sources of tablet mass variation were so small that, in general, their effect on C_t was within the confidence interval of C_{Rt}.

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Glossary

Symbol	Meaning
a (subscript)	parameter of the coarse constituent A
a	mean proportion by mass of A per sample
a_v	mean proportion by apparent volume of A per sample
A	coarse constituent of high working density
b (subscript)	parameter of the fine constituent B
$b = 1 - a$	mean proportion by mass of B per sample
$b_v = 1 - a_v$	mean proportion by apparent volume of B per sample
B	fine constituent of low working density
C_R	coefficient of variation of the mean content of a constituent per sample (tablet) of the random mixture ('random content variation')
C_{Rt}	coefficient of variation as a percentage of the mean mass of samples of constant volume V drawn from the random mixture ('composition-dependent random variation of tablet mass')
C_t	coefficient of variation of the tablet mass found
$\bar{d}_v$	volume-weighted/volume-number mean particle diameter
F	volume shape factor of the particles
k_w	density coefficient
$\overline{M}$	mean tablet mass
Q_w	quotient of the working densities ρ_w of A and B
σ	particle density
ρ_w	working density (bulk density in the die); working density of the mixture of A and B
σ_R	standard deviation of the sample composition of the random mixture in terms of the proportion of the apparent sample volume V
$\bar{v}$	representative mean particle volume of a constituent
V	constant sample volume (die volume)