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Report

Particle Size and Content Uniformity

Samuel H. Yalkowsky[1,2] and Sanford Bolton[3]

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The requirements of the USP Content Uniformity test are translated into physical and mathematical parameters. Assuming spherical particle sizes with a log normal distribution, the mean particle size and particle size distribution required to insure a high probability of passing the content uniformity test are calculated. On the basis of these calculations it is shown that satisfactory tablets of low doses cannot be manufactured from a drug that does not meet certain particle size distribution specifications. It is recommended that particle size specifications for low dose drugs include a requirement for a limit to size distribution.

KEY WORDS: content uniformity; particle size; distribution; uniformity; probability; tablets.

INTRODUCTION

If a low-dose (<100-μg) drug is to be formulated as a tablet, it is critical that the drug be uniformly distributed among the tablets. This problem must be faced more frequently as more potent drugs are developed. The following is an attempt to calculate the minimum number of particles and the maximum mean particle size required to ensure a 99% probability of passing the USP Content Uniformity test.

CALCULATIONS AND DISCUSSION

The USP Content Uniformity test (5) is intended to ensure that the active ingredient is distributed uniformly among the individual units of a batch. The monograph for tablets states,

> Where a Content Uniformity test is required, select a sample of 30 . . . tablets. . . . Assay 10 of these individually as directed in the Assay in the monograph, unless otherwise directed under Content Uniformity. . . .
>
> The requirements are met if the content of each of the 10 tablets is within the limits of 85.0 percent and 115.0 percent of the average of the limits specified in the potency definition in the individual monograph.
>
> If the content of not more than 1 tablet falls outside the limits of 85.0 percent and 115.0 percent and if the content of none of the tablets falls outside the limits of 75.0 percent and 125.0 percent of that average, assay each of the remaining 20 tablets. The requirements are met if the content of each of the additional 20 tablets falls within the limits of 85.0 percent and 115.0 percent of the average of the limits specified in the potency definition in the individual monograph, unless otherwise stated in the individual monograph.

From the binomial distribution, for a random sample of 30 tablets, the probability P of passing the Content Uniformity test is

$$P = P_1^{10} + (10P_1^9P_2)P_1^{20} = P_1^{10}(1 + 10P_2P_1^{19}) \quad (1)$$

where P_1 is the probability of a tablet being between 85 and 115% of the mean potency and P_2 is the probability of a tablet falling outside of this range but between 75 and 125% of the mean.

$$P_1 = \text{Prob}(0.85 < x < 1.15) \quad (2)$$

and

$$P_2 = \text{Prob}(0.75 < x < 1.25) - P_1 \quad (3)$$

The value of x in Eqs. (2) and (3) is given by

$$x = \frac{T}{T_o} \quad (4)$$

where T is the total weight of drug in a tablet and T_o is the label potency. If the mean value of T is T_o, then

$$E(x) = 1 \quad (5)$$

where $E(x)$ represents the population mean of x.

For any given probability P of passing the Content Uniformity test (e.g., $P = 0.99$) Eqs. (3)–(5) can be solved for the value of P corresponding to a given variance of x if the probability distribution of x is known.

Because of the large number of particles involved, we assume that x follows a normal distribution with a mean of unity and a variance of var, i.e.,

$$f(x) = N(1,\text{var}) \quad (6)$$

Using International Mathematical Society Library subroutines, Eqs. (1) through (5) can be solved to find var for any given value of P, the probability of passing the content uniformity test. Table I shows the maximum variance associated with several probabilities.

P can be calculated, given the variance. For example,

[1] College of Pharmacy, University of Arizona, Tucson, Arizona 85721.

[2] To whom correspondence should be addressed.

[3] St. John's University, Jamaica, New York 11439.

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Table I. Maximum Variance Associated with Various Probabilities

P	σ_2 (var)
0.9	4.437 E-3
0.95	3.889 E-3
0.99	3.064 E-3
0.999	2.370 E-3

with variance 4.437 E-3, $P_1 \approx 0.976$ and $P_2 \approx 0.024$ [from Eqs. (2) and (3)]. Substituting these values into Eq. (1) results in $P = 0.9$. Figure 1 shows a plot of P vs var which can be used to estimate P for a given value of var (or vice versa).

The variances in Table I can be related to the distribution of *particle size* for the active ingredient and to the distribution of the *particles among* the tablets. In order to do this, two assumptions were made.

(1) The particle diameters are distributed according to a log normal distribution having a coefficient of variation of C (fraction).

(2) The number of particles per tablet is governed by a Poisson distribution, with the mean number of particles per tablet equal to θ.

From these conditions it can be shown (see Appendix) that the variance of x, Var (x), is

$$\text{Var}\,(x) = \frac{(1 + C^2)^9}{\Theta} \tag{7}$$

In order to meet any of the probabilities of Table I, the variance of x mut be less than or equal to the value of var given in the table, i.e.,

$$\text{Var}(x) \leqslant \text{var} \tag{8}$$

and thus

$$\Theta \geqslant \frac{(1 + C^2)^9}{\text{var}} \tag{9}$$

The solution to Eqs. (1)–(3) (examples of which are given in Table I) can be combined with Eq. (9) so that any probability of passing the USP Content Uniformity test can be related to

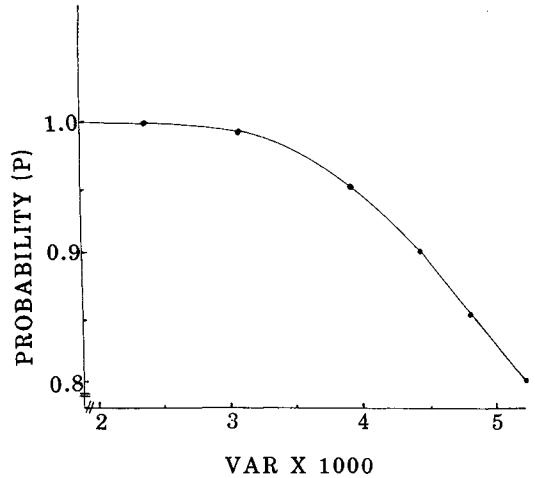

Fig. 1. Plot of the probability of passing the content uniformity test as a function of the variance of (total drug in tablet/label potency).

Θ, the mean number of particles per tablet, and C, the coefficient of variation of particle diameters. Table II gives minimum values of Θ required for a 99% probability of passing the content uniformity test for particle distributions having $0\% < C < 200\%$.

Analysis of moments indicates that there is considerable departure from the assumed normal distribution for $C \geqslant 50\%$. Since the error introduced by this deviation is to underestimate Θ, we can still regard the calculated values as meaningful and as indicating that at least that number of particles is required.

The maximum mean particle diameter m associated with any value of Θ will depend upon the dose, the particle density, and the particle geometry. To facilitate the calculations we assume spherical particles of unit density. The specified dose on micrograms is then equal to the total particle volume, V_o, in thousandths of microliters. The mean particle volume v_{req} that is required is

$$v_{req} = \frac{V_o}{\Theta} \tag{10}$$

The assumptions made in this treatment tend to underestimate the number of particles required. They therefore overestimate the required particle size so that the estimates obtained are truly maximum acceptable mean particle sizes.

Analysis of Eq. (1) shows that small variations in P_1 result in large changes in P; also, in any actual (as contrasted with theoretical) distribution the values of P_1 and P_2 cannot be determined with a high precision. Therefore, the present solution represents an approximation under certain assumed theoretical conditions.

The total volume of drug required to give dose T_o (μg) is

$$V_o = T_o/D = 10^6\, T_o \qquad (\text{units } \mu\text{m}^3) \tag{11}$$

where density is assumed to be $D = \text{g/cm}^3$.

Equating the mean total volume to V_o,

$$\Theta v_p = V_o \tag{12}$$

and for a given mean particle volume, the mean number of particles is

$$\Theta = V_o/v_p \tag{13}$$

In the analysis, the distribution of $X = T/T_o$ has been approximated by a normal distribution with mean = 1 and variance $(1 + C^2)9/\Theta$. It can be shown that, as $\Theta \to \infty$, the distribution of the standardized variable

$$\frac{(x - 1)\sqrt{\Theta}}{(1 + C^2)^{9/2}} \tag{14}$$

converges to the normal distribution $N(0, 1)$. Convergence to the normal will be slow for large C. Moreover, Θ cannot be increased without limit but is determined by Eq. (13). Calculations of the standardized third and fourth moments of the X distribution (2) for $C > 0.5$ and Θ at its lower limit show that, in this situation, the distribution is quite nonnormal. However, the results obtained with the normality assumption are still useful approximations and Eq. (9) appears to give a limit to Θ which is less than would occur with the actual distribution.

Table II. Maximum Mean Particle Diameter (μm) and Associated Coefficient of Variation Which Assures a 99% Probability of Passing the USP Content Uniformity Test

Particle diameter coefficient of variation, C (%)	Minimum mean number of particles, θ	Dose					
		0.1 μg	1 μg	10μg	100 μg	1 mg	10 mg
		Maximum mean diameter (μm)					
0	3.27×10^2	8.36	18.0	38.8	83.6	180.0	388.0
20	4.64×10^2	7.15	15.4	33.2	71.5	154.0	332.0
40	1.24×10^3	4.62	9.95	21.4	46.2	99.5	214.0
60	5.19×10^3	2.44	5.27	11.3	24.4	52.7	113.0
80	2.80×10^4	1.16	2.49	5.37	11.6	24.9	53.7
100	1.67×10^5	0.523	1.13	2.43	5.23	11.3	24.3
120	1.00×10^6	0.236	0.508	1.10	2.36	5.08	11.0
140	5.69×10^6	0.109	0.235	0.506	1.09	2.35	5.06
160	3.00×10^7	0.0521	0.112	0.242	0.521	1.12	2.42
180	1.45×10^8	0.0259	0.0558	0.120	0.259	0.558	1.20
200	6.37×10^8	0.0134	0.0288	0.0621	0.134	0.288	0.621

The distribution problem has been studied in more detail but only the essential results are reported here.

Since we have assumed a log normal distribution of spherical particle diameters, the mean particle volume V_p, in terms of the mean particle diameter m and the coefficient of variation C, is

$$V_p = \frac{\Pi}{6} m^3(1 + C^2)^3 \tag{15}$$

The mean required particle diameter can be calculated by equating the actual particle volume with the required particle volume, i.e., $V_p = V_{req}$. This gives (see Appendix)

$$m < (6 \text{ var}/\Pi)^{1/3} (1 + C^2)^{-4} V_o^{1/3} = 10^2 (6 \text{ var}/\Pi)^{1/3} (1 + C^2)^{-4} T_o^{1/3} \tag{16}$$

m represents an upper limit for mean particle diameter for a given C and T_o.

It is clear from Eq. (15) that the maximum value of m increases with the cube root of the dose if C is held constant. The calculated maximum mean particle diameters for doses of 0.1, 1, 10, and 100 μg and 1 and 10 mg are given in Table II. It is clear from the tables that m is highly dependent on both the dose and the uniformity of the particle sizes.

By rearranging Table II we can calculate the minimum tablet dose that can be manufactured from a powder whose mean particle size and coefficient of variation are known. This is done in Table III for various combinations of these parameters. An illustration of the calculation follows.

From Eq. (16),

$$T_o \geq 10^{-6} \frac{\Pi}{6} \frac{m^3}{\text{var}} (1 + C^2)^{12}$$

From Table I, var = 3.064×10^{-3} for $P = 0.99$, $m = 10^{-3}$ cm, and $C = 1$,

$$T_o \geq \frac{\Pi}{6} \frac{10^{-9}}{3.064 \times 10^{-3}} \cdot 2^{12} = 700 \times 10^{-6} \text{ g}$$

It is apparent from the tables that the mean particle size alone does not always provide enough information to determine the acceptability of a lot of bulk drug. For the manufacture of low-dose tablets it is necessary to ensure a relatively uniform size distribution as well as a mean particle size.

The most effective means of reducing the particle size of powders is micronization. Unfortunately micronization is

Table III. Minimum Average Dose as a Function of Mean Particle Diameter and Coefficient of Variation Which Assures a 99% Probability of Passing the USP Content Uniformity Test

CV (%)	Mean particle diameter (μm)						
	1	2	5	10	20	50	100
0	0.17 ng	1.4 ng	21.0 ng	170.0 ng	1.4 μg	21.0 μg	170.0 μg
20	0.27 ng	2.2 ng	34.0 ng	270.0 ng	2.2 μg	34.0 μg	270.0 μg
40	1.0 ng	8.1 ng	130.0 ng	1.0 μg	8.1 μg	130.0 μg	1.0 mg
60	6.8 ng	55.0 ng	860.0 ng	6.8 μg	55.0 μg	860.0 μg	6.8 mg
80	65.0 ng	520.0 ng	8.1 μg	65.0 μg	520.0 μg	8.1 mg	65.0 mg
100	700.0 ng	5.6 μg	87.0 μg	700.0 μg	5.6 mg	87.0 mg	700.0 mg
120	7.6 μg	61.0 μg	950.0 μg	7.6 mg	61.0 mg	950.0 mg	7.6 g
140	77.0 μg	620.0 μg	9.7 mg	77.0 mg	620.0 mg	9.7 g	77.0 g
160	710.0 μg	5.7 mg	89.0 mg	710.0 mg	5.7 g	89.0 g	710.0 g
180	8 mg	46.0 mg	720.0 mg	5.8 g	46.0 g	720.0 g	5.8 kg
200	42.0 mg	300.0 mg	5.2 g	42.0 g	330.0 g	5.2 kg	42.0 kg

not suitable for all drugs. The frictional heat produced in micronizing can cause some drugs to soften or melt and then agglomerate. The same heat can cause thermally unstable drugs to degrade. Even the smallest micronizer consumes up to 50 g of drug in bringing the machine up to full speed. This makes micronization unacceptable for drugs which are available in limited quantities.

The most common means of reducing particle size is milling. Depending on the type of mill and the nature of the drug, milling can produce particle sizes anywhere between 50 and 1000 μm. It is clear from Table III that unless the particles are monodisperse, milling cannot be used for drugs given in less than 100 μg per tablet. Realistically assuming a relatively uniform distribution of sizes having a 50% coefficient of variation and a mean particle size of 100 μm (140 U.S. standard mesh), milling is borderline for doses below 10 mg.

It is difficult to generalize on either the mean particle size or the particle size distribution produced by micronization. The physical properties of the powder play an extremely important role in determining the extent of its communication. Frequently 5- to 20-μm particles are produced by micronization; however, for some materials, particles as small as 1 μm can be obtained, and for others it is not possible to produce particles below 30 μm. Some materials, because of a low melting point or low thermal stability, cannot be micronized at all. Size distributions of micronized particles also vary widely, with coefficients of variation ranging from 35 to over 200%.

If the distribution of particle sizes is uniform (CV <50%) and if the mean particle size is below 5 μm, then micronization can be used to produce material suitable for incorporation into tablets with doses as low as 1 μg. In most cases the mean particle size produced by micronization is greater than 10 μm so that a 1-μg tablet cannot be manufactured. For drugs which cannot be micronized, the minimum dose that can be reliably produced can exceed 1 mg.

APPENDIX

Assumptions were as follows.

1. Particle diameters, d, are distributed independently in a log-normal distribution $\ln(\mu,\sigma^2)$ [Eq. (A1)]. Mean particle diameter, m, and coefficient of variation, C.
2. The number n of particles in a tablet is distributed by the Poisson distribution (Eq. (A7)]. Also, n and d are independent.
3. For calculation of volume, particles are assumed to be spherical.
4. Mean value of total drug per tablet, T, is equal to target or label, T_o.
5. The distribution of the ratio or dose (weight) of drug in individual tablets to the theory or label dose ($X = T/T_o$), which derives from the previous assumptions, can be approximated by a normal distribution—at least to give useful results.

Mathematical symbols and measurement units which were used are defined in Table A1.

A random variable d has a log normal distribution if $\ln d$ has a normal distribution. The log-normal density function is

Table A1. Symbols Used in the Appendix

Symbol	Units	
m	μm	Mean particle diameter
C	—	Coefficient of variation of particle diameter distribution (fraction)
P	1	Probability of passing USP test
P_1P_2	1	Defined in Eqs. (2) and (3)
T	μg	Total wt of drug in tablet (random variable)
T_o	μg	Target dose (label)
$x = T/T_o$	1	Total drug wt/target
var	1	Required variance of x to give P
var(x)	1	Variance of x
Θ	1	Mean No. of particles
V_o	μm³	Total volume of required dose (assuming density = 1 g/cm³, $V_o = 10^6\ T_o$)
V_p	μm³	Mean particle volume determined from m and C

$$f(d) = \mathrm{LN}(\mu,\sigma^2) = (1/\sqrt{2\Pi}\sigma d)\exp\left[-(\ln d - \mu)^2/2\sigma^2\right] \tag{A1}$$

where μ is the mean and σ^2 the variance of $\ln d$. The LN distribution is analyzed in detail in Ref. 1. Some characteristics of the LN function which are used in this derivation can be derived from the density function, Eq. (A1):

$$1 + C^2 = e^{\sigma^2} \tag{A2}$$

where C is the coefficient of variation.

$$E(d^k) = m^k(1 + C^2)^{k(k-1)/2} \tag{A3}$$

If

$$y = a\,d^b \tag{A4}$$

where a and b are arbitrary constants with $a > 0$, then the density of y is also LN, and

$$g(y) = \mathrm{LN}\,(\ln a + b\mu, b^2\sigma^2) \tag{A5}$$

so that, from Eq. (A2),

$$1 + C^2_y = (1 + C^2)^{b^2} \tag{A6}$$

where C_y is the coefficient of variation of y.

The Poisson density function is

$$p(n) = \frac{e^{-\Theta}x^n}{n!} \tag{A7}$$

with mean

$$E(n) = \Theta \tag{A8}$$

and variance

$$\mathrm{Var}(n) = \Theta \tag{A9}$$

The weight fraction of drug in a tablet is given by

$$x = T/T_o \tag{A10}$$

where T_o is the target or label amount and

$$T = \sum_{i-i}^{n} W_i \tag{A11}$$

is the sum of weights (w_i) of the n individual particles.

T is the sum of a random number (n) of independent random variables (w). This type of sum is considered in the probability literature (3,4).

For such a sum, it can be shown that

$$E(T) = E(n)E(w) \tag{A12}$$

$$\text{Var}(T) = E(n)\ \text{Var}(w) + \text{Var}(n)\ [E(w)]^2 \tag{A13}$$

By assumption 4,

$$E(T) = T_o \tag{A14}$$

so that

$$E(x) = 1. \tag{A15}$$

From Eqs. (A12) and (A13),

$$E(T) = \Theta\ E(w) \tag{A16}$$

$$\text{Var}(T) = \Theta\ [E(w)]^2(1+C_w^2) \tag{A17}$$

$$\text{Var}(x) = (1 + C_w^2)/\Theta \tag{A18}$$

where C_w is the coefficient of variation of w.

For spherical particles

$$w = D(\Pi/6)d^3 \tag{A19}$$

where D is density.

From Eq. (A6), if a variable d has a log-normal distribution with CV = C, then the variable $y = ad^b$ is also log-normal with CV = C_y, such that $(1 + C^2_y) = (1 + C^2)^{b^2}$. From Eq. (A19),

$$w = ad^b$$

where

$$a = \frac{D\Pi}{6} \quad \text{and} \quad b = 3$$

$$\therefore (1 + C_w^2) = (1 + C^2)^9 \tag{A20}$$

Therefore,

$$\text{Var}(x) = (1 + C2)^9/\Theta \tag{A21}$$

The probability of passing the USP content uniformity test is given by Eq. (1). If X follows the normal distribution with given mean [$E(X) = 1$], then Eqs. (1)–(3) can be solved numerically for the maximum variance var (Table I). The minimum mean number of particles Θ is then determined by Eqs. (8) and (9).

Equation (16) is derived as follows:

$$V_p = \frac{\Pi}{6} m^3 (1 + C^2)^3 \qquad \text{[from Eq. (11)]}$$

$$V_{rep} = \frac{V_o}{\Theta} \qquad \text{[from Eq. (10)]}$$

$$= \frac{V_o\ \text{Var}(x)}{(1 + C^2)^9} \qquad \text{[from Eq. (7)]}$$

$$\leq \frac{V_o\ \text{var}}{(1 + C^2)^9} \qquad \text{[from Eq. (8)]}$$

Therefore $V_p = V_{rep}$ gives

$$\frac{\Pi}{6} m^3 (1 + C^2)^3 \leq \frac{V_o\ \text{var}}{(1 + C^2)^9} \qquad (V_o = 10^{-9}\ L)$$

or

$$m^3 \leq \frac{6\ V_o\ \text{var}}{\Pi} (1 + C^2)^{-12}$$

or

$$m \leq \left(\frac{6\ \text{var}}{\Pi}\right)^{1/3} (1 + C^2)^{-4} V_o^{1/3}$$

where

$$V_o = 10^6\ T_o \qquad (T_o = \text{grams})$$

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