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Effect of drug particle size on content uniformity of low-dose solid dosage forms

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Abstract

Two low-dose blends were prepared that differed only in the particle size of the drug used to make the blends. The geometric mean particle diameters for the two lots of drug used were 18.5 and 6.1 μm. Samples of the blends approximately equivalent to the unit dose of 10 μg per 99 mg of blend were assayed for potency. For the blend containing the larger particle size drug, the potency range was 88–130% ($n = 65$) compared to 97–102% ($n = 64$) for the blend containing the smaller particle size drug. A simple computer method was able to qualitatively simulate the observed potency profiles using only the particle size distribution of the drug and assuming ideal mixing. The method provides guidance in setting particle size specifications to avoid poor content uniformity. © 1997 Elsevier Science Ireland Ltd.

Keywords: Content uniformity; Particle size; Low-dose; Computer simulation

1. Introduction

For low-dose solid dosage forms, individual drug particles that are generated from conventional milling methods can be large enough to represent a significant portion of the dose. These large particles can be present in a blend in numbers too low to be found in every unit dose. When one or more of these particles are found in a single unit dose, the observed potency can fall outside the desired potency limits. This problem cannot be solved by mixing, and the larger drug particles must be reduced in size before attempting to make a homogeneous blend.

The effect of particle size on content uniformity has been discussed in the literature (Yalkowsky and Bolton, 1990). However, it requires a sophisticated understanding of statistics and no experimental data was provided to test the analysis given.

The objective of the current work was to demonstrate the effect of drug particle size on the

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content uniformity of a low dose drug-excipient blend, and to show that simple calculations could be made to simulate the results. This was done to help validate a computational method that would provide guidance in setting particle size specifications to avoid poor content uniformity.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel PH 102) was obtained from the FMC Corporation, Philadelphia, PA. Calcium phosphate dibasic, anhydrous was obtained from Rhône-Poulenc Basic Chemicals Company, Chicago Heights, IL. Sodium starch glycolate (Explotab) was obtained from Mendell, Patterson, NY. CP-118 954 is a potent inhibitor of acetylcholinesterase for the treatment of cognitive disorders (Villalobos et al., 1995) and was manufactured as the maleate salt at the Pfizer Central Research facility in Groton, CT.

2.2. Methods

2.2.1. Blend preparation

Two blends were prepared that differed only in the particle size of the drug used to make the blends. Table 1 shows the nominal composition of the unit dose along with the batch size. Microcrystalline cellulose, dibasic calcium phosphate, and sodium starch glycolate were passed through an 80 mesh screen before use. The three excipients were then blended together in a 400-ml amber-glass round-bottom bottle for 1 h using a Turbula T 2 C mixer at middle speed, and the excipient blend was set aside. The excipient blend (3 g) was added together with CP-118 954 in a mortar and the combination was gently mixed with a pestle for 2 min. The resulting drug blend was transferred to a separate 400 ml amber-glass round-bottom bottle. The weighing paper used to weigh the drug and the mortar was flushed with 10 g of the excipient blend, and the resulting blend was added to the drug blend. The rest of the excipient blend was added to the drug blend. The final blend was mixed 3 times for 1 h using the Turbula mixer. After each 1-h mixing period, the blend was passed through a 60 mesh screen. Finally, the blend was mixed for 2 h before the blend was assayed for content uniformity.

Table 1
Nominal composition of drug-excipient blends

Component	mg/dose	mg/batch
CP-118 954	0.010	13.75
Microcrystalline cellulose	64.990	89 361.25
Calcium phosphate dibasic, anhydrous	32.000	44 000.00
Sodium starch glycolate	2.000	2750.00

2.2.2. Assay of blend samples

Approximately 100 mg of drug blend were accurately weighed and transferred to a 10-ml volumetric flask. Mobile phase was added to the volumetric flask to bring the volume to the mark, and the flask was placed in a sonic bath (Branson 5200) and sonicated for 10 min. The flask was inverted 10 times, and the contents were filtered through a 0.2-μm filter (Nylon Acrodisc, 13 mm), discarding the first 2 ml. Following this, 50 μl of the filtered solution was injected onto HPLC using an auto-injector (Bio Rad Model AS-100 HRLC). The rest of the HPLC system consisted of an HPLC pump (Thermo Separation Products, constaMetric 3200), a reverse phase column (Waters Nova-Pak C_{18} 3.9 × 150 mm), a variable wavelength detector set at 210 nm (Applied Biosystems, 785A), and an integrator (Thermo Separation Products, ChromJet). The mobile phase consisted of 80% 0.02 M potassium phosphate monobasic in water, 20% acetonitrile, and 0.2% triethylamine with the final pH adjusted to 3.5 with phosphoric acid. The flow rate was 1 ml/min with an approximate retention time of 5 min for CP-118 954.

2.2.3. Milling of drug substance

Two lots of CP-118 954 were used for the study. One lot was milled using a Bantam mill (Bantam Mikro-Pulverizer, Pulverizing Machinery, Summit, NJ) fitted with a 0.02-inch herringbone screen with hammers rotating at 14 000 rpm. The second

lot was generated by milling the same Bantam-milled lot using a model 00 Jet-O-Mizer (Fluid Energy Aljet, Plumsteadville, PA) with nitrogen gas at a pressure of approximately 90 psi.

2.2.4. Measurement of drug particle size

A Coulter Multisizer II (Coulter Electronics, Hialeah, FL) was used to measure drug particle size. The electrolyte was made by adding 40 g of maleic acid (Sigma) to 2 l of water. The pH was adjusted to 5.4 with a 50% w/w sodium hydroxide solution (Fisher Scientific). Tween 80 (0.1 g) (NF grade, ICI Americas) were added and the entire solution was saturated with CP-118 954 and left to equilibrate overnight. The suspension was filtered two times through 0.45-μm filters (Nylon-66, Rainin) and once through a 0.22-μm filter (GVWP 047, Millipore). The particle size distributions of the Bantam-milled and Jet-milled lots were measured using 200 and 140-μm aperture tubes, respectively.

2.2.5. Density measurement

The true density of CP-118 954 was measured to be 1.3 g/cc using a micropycnometer (Quantachrom model MPY-2, Syosset, NY).

2.2.6. Computer simulation of potencies

A computer method described below simulates the entire number, size, and mass of drug particles expected to be found in a batch of solid dosage forms based on the drug particle size distribution. The program then distributes the drug particles evenly across all unit doses.

Depending on the drug particle size distribution, larger drug particles may be present in the batch in numbers too low to be found in every unit dose. These particles are added to unit doses at regular intervals to maintain a mass balance of drug for the entire batch. The amount of drug in each unit dose is then calculated by adding up the mass of each particle in the unit dose.

The maximum and minimum particle size radii of a simulated particle size distribution, r_{max} and r_{min}, respectively, were calculated as follows:

$$r_{max} = r_{mean}\sigma_g^x \quad (1)$$

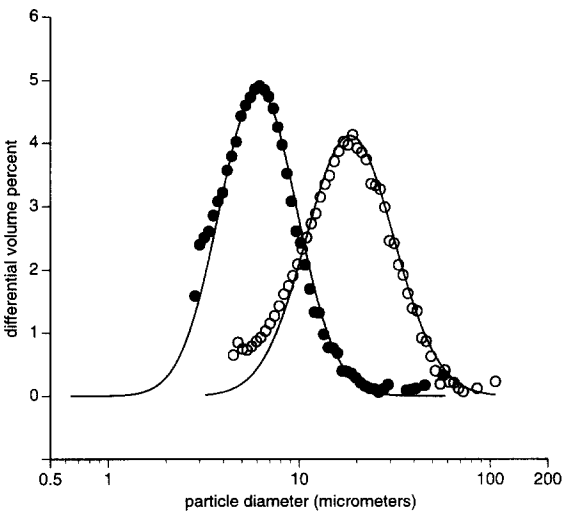

Fig. 1. Particle size distributions of Bantam-milled drug (○) and Jet-milled drug (●). Simulated lines were drawn using geometric mean particle sizes of 18.5 and 6.1 μm and geometric standard deviation of 1.7 and 1.6 for the Bantam and Jet-milled drug, respectively.

$$r_{min} = \frac{r_{mean}}{\sigma_g^x} \quad (2)$$

where r_{mean} is the geometric mean particle size radius and σ_g is the geometric standard deviation. x was set equal to 3.3 for the Bantam-milled drug and to 4.8 for the jet-milled drug, allowing the upper particle size of the simulated distributions to match the experimental data. As shown in Fig. 1, geometric means of 18.5 and 6.1 μm, and geometric standard deviations of 1.7 and 1.6 were used to simulate the particle size data of Bantam-milled and Jet-milled CP-118 954 respectively. To make the peak of the simulated distributions match the experimental data in Fig. 1, 65 and 80 particle size groups were used for the Bantam-milled and Jet-milled drug, respectively. However, when simulated distributions were used to simulate potency values, 100 particle size groups were used for both Bantam and Jet-milled CP-118 954.

The particle size-mass distribution was generated using the log-normal function:

$$\text{mass}_i = \frac{1}{\ln \sigma_g \sqrt{2\pi}} \exp\left(-\frac{1}{2}\left[\frac{\ln(r_i/r_{mean})}{\ln \sigma_g}\right]^2 \right) \quad (3)$$

where mass_i is the total mass of all particles with a radius of r_i, r_i was calculated as follows:

$$r_i = \exp(r_{inc}(i-1) + \ln(r_{min})) \quad (4)$$

were r_{inc} is the evenly spaced increment on a log scale given by:

$$r_{inc} = \frac{\ln(r_{max}/r_{min})}{99} \quad (5)$$

where i varied from 1 to 100 in the present simulations.

The unit dose-normalized mass $mass_{ni}$ of drug in each particle size fraction was calculated as follows:

$$mass_{ni} = \frac{mass_i}{\sum_{i=1}^{100} mass_i} \times dose$$

The volume v_i and mass m_i of a single particle of radius was calculated as follows:

$$v_i = \frac{4}{3}\pi r_i^3 \quad (7)$$

$$m_i = v_i \rho \quad (8)$$

where ρ is the drug density.

The total number of particles n_i of radius r_i in a single unit dose is given by:

$$n_i = \frac{mass_{ni}}{m_i} \quad (9)$$

Once n_i and m_i were defined, the following programming logic was used to simulate the potencies of one million unit doses:

for $j = 1$ to 1 000 000

for $i = 1$ to 100

if $n_i > 1$ then potency = potency + $n_i * m_i$

if $n_i < 1$ then $g_i = g_i + n_i$

if $g_i > 1$ then potency = potency + m_i

if $g_i > 1$ then $g_i = 0$

next i

print potency

potency = 0

next j

g_i serves as a counter that distributes particles at regular intervals throughout the batch for particles that occur less frequently than one per unit dose.

3. Results and discussion

The experimentally determined potency data are shown in Table 2. The average potency of the blend made with Bantam-milled drug was 101.2% with a R.S.D. of 6.3% ($n = 65$) compared to the blend made with Jet-milled drug which had an average potency of 99.8% with a relative standard deviation of 1.1% ($n = 64$). The blend containing the larger particle size Bantam-milled drug displayed a much larger range of potencies than the smaller drug particle size blend.

Also shown in Table 2, the experimental results could be qualitatively predicted by computer simulations as described in Section 2.2.6. The simulations were also able to predict the experimentally observed skewness of the data toward higher potencies.

The advantages in using the log-normal function to characterize particle size data include the ease of expressing particle size distributions and the speed of simulating data. However, the analysis presented here does not require that particle size distributions follow a log-normal distribution, and any function that simulated the data could be used.

In comparing the experimental and simulated potency data in Table 2, the observed frequency of very high potency values was greater for the experimental data. This indicates that real mixing is not as good as that simulated by the program. Therefore, simulations that predict good homogeneity only show that good content uniformity is possible if mixing is close to ideal. However, this analysis is useful in determining whether drug particle size or mixing is responsible for poor content uniformity. It should be noted that reducing particle size in an attempt to improve content uniformity may not work if at the same time, it increases the tendency of the drug particles to aggregate.

Table 2
Experimental and simulated percent of intended potency profiles of drug-excipient blends made with either the larger Bantam-milled drug or the smaller Jet-milled drug. The intended potency was 10 μg

Percent of intent	Number of unit doses within the given percent of intent range			
	Experimental		Simulated	
	Bantam	Jet	Bantam	Jet
70–74				
74–78				
78–82				
82–86				
86–90	1			
90–94	5			
94–98	13	5	483 249	
98–102	20	59	313 436	1000 000
102–106	16		145 337	
106–110	7		45 537	
110–114	1		9744	
114–118			2191	
118–122	1		447	
122–126			58	
126–130	1		1	

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