Physical Characterization of Large Porous Particles for Inhalation

To the Editor:

In a recent study by Vanbever et al. (1), the authors claimed several advantages of using large, porous particles for drug delivery to the lungs. While it is true that the spray dried particles discussed in this paper appeared to have low densities, and that low particle density confers small aerodynamic size upon geometrically large particles, the usefulness of powders in inhalation therapy depends upon their aerodynamic size characteristics following dispersion. Unfortunately, the author's claim (1) to have "compared [and correlated] the aerodynamic size and [aerosol] performance of their particles with theoretical estimates based on bulk powder measurements" is based on incorrect theory and frail measurement techniques.

Vanbever et al. (1) computed values for the theoretical Mass Mean Aerodynamic Diameter, MMADt, based upon experimental measures of geometric diameter and bulk powder density. Following this, they created aerosols from their powders and used both cascade impaction and an Aerosizer, to determine the Mass Median Aerodynamic Diameter, MMADe, of the particle clouds. Although there was minimal relation between MMADe and MMADt following the benchmark method [cascade impaction showed *average* MMADe to be approximately twice *average* MMADt], the Aerosizer data showed almost a 1:1 correlation between the two variables [Table 1, Fig 6c (1)]. The authors use this positive correlation to support the relevance of theoretical values for MMADt, as aerosol performance indicators for their powders. Because it is well known that Mass Mean and Mass Median Aerodynamic Diameters for aerosols and log—normally distributed powders only equate under conditions of monodispersity, this approach is theoretically incorrect. For polydisperse systems with known geometric standard deviations, GSD, the ratio of Mass Mean/Mass Median Aerodynamic Diameter can be computed from the Hatch-Choate conversion equation (2) using:

$$\frac{\text{Mass Mean Aerodynamic Diameter}}{\text{Mass Median Aerodynamic Diameter}} = \exp\,[0.5\ \ln^2 \text{GSD}] \quad (1)$$

The authors failed to report the dispersity of their powders but values for GSD up to 3.0 are common; corresponding to an MMADt/MMADe ratio of about 1.8. Even for a low GSD value of 2.0, the MMADt/MMADe ratio is 1.3. Thus, if the author's calculations for MMADt are to be useful in the calculation of MMADe, assuming a GSD of 3.0, values for MMADt of approximately 12 and 7 would be required in order to predict this paper's experimental results for cascade impaction and Aerosizer, respectively. The author's *average* reported value for MMADt of approximately 3.2 is a clear indication of the fundamental inadequacy of the author's theory to explain their experimental results.

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2. W. C. Hinds. *Aerosol Technology—Properties, Behavior, and Measurement of Airborne Particles,* John Wiley & Sons, Inc., 1999.

Authors reply:

In their letter, Gupta and Byron make a number of erroneous assumptions, and as a consequence reach incorrect conclusions. Specifically: 1) Gupta and Byron wrongly assume that the porous powders studied by Vanbever et al. (1) possessed a significant polydispersity, with GSD values around 3.0. In fact, the porous powders produced were nearly monodisperse, with GSD values around 1.5; 2) Gupta and Byron deduce, based on their assumption of significant polydispersity, that the ratio of mean to median aerodynamic diameters for the porous powders studied by Vanbever et al. (1) was about 1.8. In fact, they grossly overestimate the ratio of mean to median (geometric and) aerodynamic diameters. The actual ratio was characteristically between 0.9 and 1.0; 3) Based on their incorrect conclusions regarding polydispersity, GSD and median/mean ratios, Gupta and Byron deduce that the theoretical estimates of mean aerodynamic diameter of the porous powders must differ grossly from the experimental (Aerosizer) mean aerodynamic diameters, although Vanbever et al. (1) report a good correlation between theory and experiment. In fact, since median and mean diameters are nearly the same, whether expressed in terms of mean or median aerodynamic diameter, the theoretical estimates of Vanbever et al. (1) closely match the experimental (Aerosizer) data, as reported.

To clarify these points, Fig. 1 depicts the size distribution of a particular individual powder represented in Table I of Vanbever et al. (1). (The size distribution of other powders is available on request.) The ratio of median to mean diameter is approximately 1.1 (or less), within the range of experimental error (see again Table 1), reflecting a GSD in the range of 1.5. Compilation of the GSD values of 49 porous powders prepared as described by Vanbever et al. (1) can be found in the thesis "Aerosol properties of large, porous particles for inhalation" (Jackie Nice, Penn State University, Department of Chemical Engineering, Honor's Thesis, 1998) (see Appendix B). The average GSD of these 49 powders is approximately 1.58. In fact, GSD values in this range are quite common for inhaled aerosols (see, e.g. Bell et al. (2), Ferrin et al. (3), and Biddiscombe et al. (4)); indeed it is surprising that Gupta and Byron assumed otherwise.

We finally note that since publication of Vanbever et al. (1) other data have appeared supporting this publication's conclusions. Gayeski et al. (5) compared cascade impaction and Aerosizer measurements of median aerodynamic diameter with theoretical predictions of median aerodynamic diameter. Cascade impaction and Aerosizer measurements yielded MMADe values of 4 to 6 μm and 3 to 4 μm, respectively, for porous powders. Theoretical estimates of mass median aerodynamic diameter, based on tap density and median

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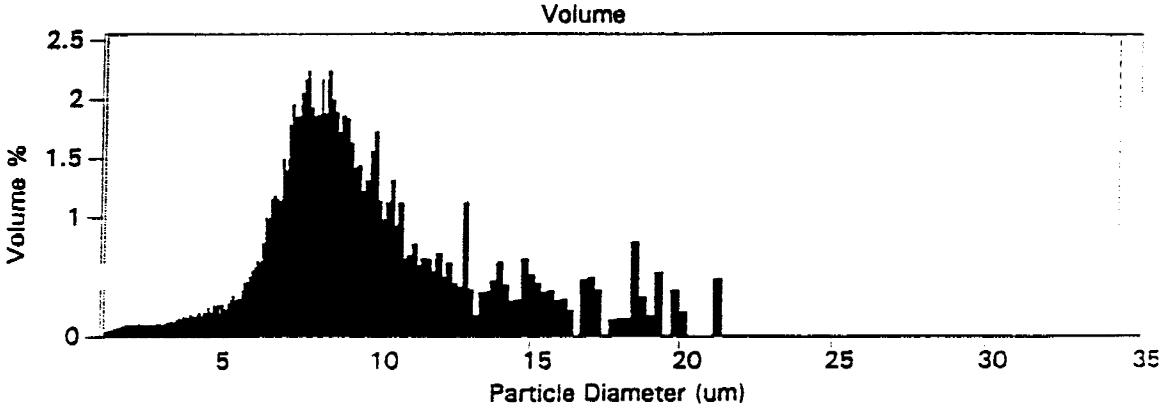

LC = 1.101 um UC = 34.27 um {100.0%}

Volume Statistics (Geometric) Untitled

Calculations from 1.101 um to 34.27 um

Volume	100.0%		
Mean:	7.889 um	95% Conf. Limits:	7.856-7.922 um
Median:	8.215 um	S.D.:	4.92 um
Mean/Median Ratio:	0.960	Variance:	24.2 um^2
Mode:	8.391 um	C.V.:	62.4%
Spec. surf. area:	0.881 m^2/ml	Skewness:	-1.21 Left skewed
		Kurtosis:	2.7 Leptokurtic

% >	10	25	50	75	90
Size um	13.71	10.13	8.215	6.828	4.538

Fig. 1. Geometric size distribution of one of the powder samples comprising the 4% formulation in Table I of Vanbever et al. (1).

geometric size, were found to be 3 to 4 μm, similar to the results of Vanbever et al. (1). In this same study, results were presented showing that other experimental techniques prove reliable measures of aerodynamic diameter of porous particles, including, for example, indirect techniques like the multistage liquid impinger (MSLI) (which addresses issues such as particle bounce and reentrainement observed with cascade impaction with porous powders) and direct techniques, namely involving gravitational settling. Also, Scheuch et al. (6) found that porous particles with MMADe (Aerosizer) of 3.1 μm, and median geometric size 11.5 μm, when labeled with technetium and inhaled via a simple dry powder inhaler, deposited greater than 60% of the emitted dose in the lungs (as deduced by gamma camera images). This result coincides with the experimental respirable fraction estimate based on the Aerosizer measurement (see Table I of Vanbever et al. (1) for an aerodynamic diameter around 3.1 μm).

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