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Research Article

Estimating the Number of Droplets and Drug Particles Emitted from MDIs

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Abstract. The objective of this paper is to assess the number of drug particles or droplets contained in metered dose inhaler (MDI) aerosols. Equations were developed to estimate this. The number of drug particles was estimated to be as high as about 300 million for QVAR® solution MDIs and as low as 670,000 for Beclovent™ MDIs. The number of particles in MDI aerosols was shown to be highly dependent on the mass median aerodynamic diameter (MMAD) and geometric standard deviation, and to a lesser extent the total mass of the aerosol. It was demonstrated that when the number of particles are calculated assuming that the aerosol is monodisperse and using the MMAD as the particle size, the number of particles are significantly underestimated. The number of droplets atomized from HFA-134a MDIs was estimated to range from about 220 million to about 1.1 billion droplets per actuation. For solution MDIs, each of the atomized droplets contains drug and thus the number of drug particles is the same as the number of atomized droplets. However, for suspension MDI formulations many of the droplets do not contain any micronized drug particles and the number of drug particles is much lower than the number of atomized droplets.

KEY WORDS: metered dose inhaler; number of particles; size distribution.

INTRODUCTION

Metered dose inhalers (MDIs) are widely used for treatment of diseases of the lung including asthma and chronic obstructive pulmonary disease. In an MDI, drug is contained in a formulation consisting of a liquefied propellant and optionally cosolvent or other excipients such as surfactants. The drug may be dissolved in the formulation or may consist of small particles suspended in the formulation. Each time an MDI is actuated, a precise quantity of formulation is atomized into fine droplets. For solution MDIs, each atomized droplet contains drug. Once the propellant and cosolvent evaporate away, the residual particles consist of drug and any non-volatile excipients. The size of the residual particles is determined by the size of the initial droplets and the concentration of non-volatiles in the formulation (1,2). For suspension MDIs, the atomized droplets may contain no drug particles, a single drug particle, or multiple drug particles (3). Usually, the residual particle will contain surfactant that is included in the formulation to reduce flocculation of the suspended particles.

The size distribution of an MDI aerosol is a critical parameter influencing the effectiveness of the inhaler since the particle size distribution significantly influences the amount and location of deposition within the lung (4–6). In addition to the particle size distribution, the efficacy of an inhaler is related to the mass of drug in the MDI aerosol as these two factors combine to determine the total amount of drug that penetrates into the respiratory tract. The mass of drug delivered to the patient is determined by the size and number of drug particles delivered. Since smaller particles contain less mass than larger particles, aerosols with smaller particle size distributions have more particles per unit mass than aerosols with larger particles. The size distribution of drug delivered from MDIs are widely characterized using techniques such as cascade impaction. While there is a great deal of literature describing the size distribution of MDIs aerosols, the number of particles delivered from MDIs has not been extensively characterized. One reason that there is minimal literature in this area is the lack of instruments capable of effectively measuring the number of particles in the entire MDI aerosol. The objective of this investigation is to develop equations to estimate the number of droplets and drug particles contained in MDI aerosols.

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METHODS

Estimating the Number of Drug Particles in an MDI Plume

The number of particles in an MDI plume can be readily estimated if the size distribution of aerosol and the total aerosol mass in the plume is known. For an MDI aerosol, the amount of mass delivered and the size distribution of the aerosol are well characterized and carefully controlled.

For the estimates of the number of particles, the MDI aerosols were assumed to be lognormally distributed. This is usually a reasonable assumption for most MDI aerosols (2,7). Additionally, the particles were assumed to be spherical. This has been shown to be a reasonable assumption for solution MDIs (8), but is not valid for all suspension MDIs since these sometimes have irregular or needle-like drug particles.

The following equations use the theory developed by Hatch and Choate (9) and adapted by Hinds (10). For a spherical particle, the relationship between aerosol mass, M, and number of particles, N, is shown in Eq. 1, where ρ is the density of the aerosol particles or droplets, and d_m is the 'diameter of average mass'. The diameter of average mass is defined as the diameter of a particle that would have the average particle mass of all of the particles in the aerosol plume.

$$M = \frac{N\rho\pi d_m^3}{6} \tag{1}$$

The relationship between d_m and the 'count median diameter' (CMD) has been developed elsewhere (10) and is described in Eq. 2, where GSD is the geometric standard deviation of the size distribution.

$$d_m = \mathrm{CMD}\exp\left(1.5\ln^2 \mathrm{GSD}\right) \tag{2}$$

The relationship between the CMD and the mass median diameter, MMD, is described in Eq. 3.

$$\mathrm{MMD} = \mathrm{CMD}\exp\left(3\ln^2 \mathrm{GSD}\right) \tag{3}$$

Combining Eqs. 1 through 3 results in Eq. 4, which can be used to estimate the number of particles in the MDI plume.

$$N = \frac{6M\exp\left(4.5\ln^2 \mathrm{GSD}\right)}{\rho\pi(\mathrm{MMD})^3} \tag{4}$$

Often the instruments used to measure the size distribution of MDI aerosols characterize particles based on their aerodynamic diameter. The relationship between the mass median aerodynamic diameter (MMAD) and the MMD is approximated in Eq. 5, where ρ_0 is the unit density (1 g/cm^3).

$$\mathrm{MMAD} = \mathrm{MMD}\frac{\sqrt{\rho}}{\sqrt{\rho_0}} = \mathrm{MMD}\sqrt{\rho} \tag{5}$$

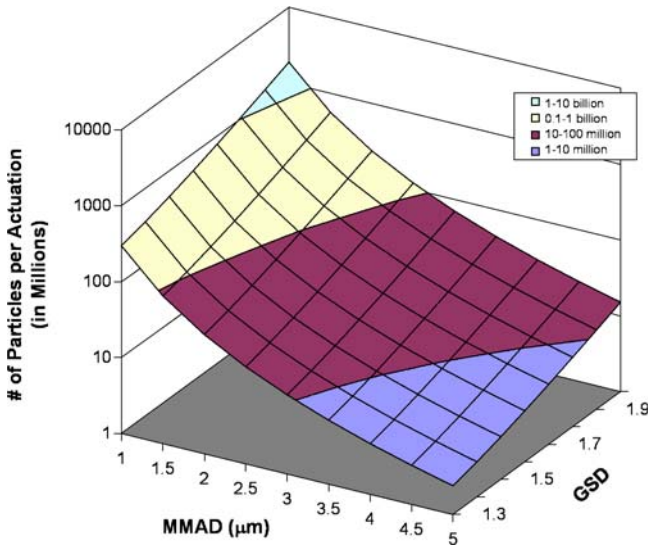

Fig. 1. The number of drug particles, calculated using Eq. 6, in theoretical MDI plumes containing 100 mcg of total drug mass

Table I. The estimated number of drug particles per actuation collected during ACI measurement of various MDI aerosols

Product Description	MMAD (μm)	GSD	M (μg/actuation)	# of Particles
QVAR®40[a,c]	0.96	1.83	22.7	290,000,000
QVAR®80[b]	1.2	1.84	45.4	300,000,000
Flixotide™ (250 μg)[a,c]	2.67	1.61	104	33,000,000
Beclovent™ (42 μg)[a,c]	4.89	1.57	14.4	670,000
Flovent® (125 μg)[b]	2.8	1.56	49.2	12,000,000
Intal® (1 mg)[b]	4.2	1.63	289	25,000,000
Proventil HFA®[d]	2.38	1.49	45.7	15,000,000

[a] Data from Stein (13)
[b] Data from Mitchell *et al.* (14; MMAD data published only to a single decimal place)
[c] MMAD and GSD values recalculated from original reference using DISTFIT™
[d] Unpublished data by author

Substituting Eq. 5 into Eq. 4 results in Eq. 6.

$$N = \frac{6M\sqrt{\rho}\exp\left(\left(4.5\ln^2 \mathrm{GSD}\right)\right.}{\pi(\mathrm{MMAD})^3} \tag{6}$$

Equation 6 can be used to predict the number of drug particles in an MDI aerosol. Often MDI size distribution parameters are determined from cascade impactor measurements. During cascade impactor testing, aggregates containing multiple micronized drug particles appear to the impactor to be a single residual drug particle. Thus, Eq. 6 will provide an estimate of the number of residual drug particles in an MDI plume and not the number of micronized drug particles.

Estimating the Number of Atomized Droplets in an MDI Plume

Equation 4 can be used to estimate the number of atomized droplets contained in an MDI plume if the size distribution of the atomized droplets is known. When Eq. 4 is used to calculate the number of atomized droplets, M is the total mass of formulation aerosolized (i.e. the 'valve delivery'), ρ is the droplet density (which can be assumed to be equivalent to the density of the formulation), and MMD and GSD describe the size distribution of the initial atomized droplets. The initial MMD and GSD used in Eq. 4 can be either from experimental measurements or theoretical calculations. However, the initial size distribution of the atomized droplets are not typically measured for MDI aerosols due to the very rapid change in size as the droplets evaporate. However, the influence of formulation and device configuration on the initial size distribution of atomized droplets from HFA-134a MDIs has been previously studied in detail (2). Equation 7 shows an empirical equation that can be used to predict in the initial droplet MMD ($\mathrm{MMD_{Initial}}$) for HFA-134a MDIs based on the actuator orifice diameter (OD) and ethanol concentration (C_{Eth}) of the formulation (2). The size distribution of the atomized droplets was shown in the previous investigation to

Table II. The number of particles in an aerosol, calculated using Eq. 6, with the same mass median aerodynamic diameters, but different geometric standard deviations

GSD	1.0	1.2	1.4	1.6	1.8	2.0
MMAD (mm)	2.5	2.5	2.5	2.5	2.5	2.5
M (mg/actuation)	100	100	100	100	100	100
# of Particles	14,000,000	16,000,000	23,000,000	38,000,000	66,000,000	121,000,000

be independent of valve size, so Eq. 7 can be used regardless of the size of the valve on the MDI configuration being evaluated. The GSD of atomized droplets from HFA-134a MDIs was assumed to be about 1.8 based on previous work (2).

$$\mathrm{MMD}_{Initial} = 11.0 - (7.80 \times C_{Eth}) - (20.0 \times OD) + \left(67.6 \times C_{Eth}^2\right) + \left(26.5 \times \mathrm{OD}^2\right) + (39.8 \times C_{Eth} \times \mathrm{OD}) \quad (7)$$

For the estimations in this paper of the number of atomized droplets, Eq. 7 was used to estimate the initial droplet MMD for HFA-134a MDI configurations. The density of the formulation, ρ, was estimated using Eq. 4 from Stein & Myrdal[2]. Then, Eq. 4 from this paper was then used to calculate the number of atomized droplets assuming the GSD was 1.8.

RESULTS AND DISCUSSION

Estimating the Number of Drug Particles in an MDI Plume

Equation 6 was used to calculate the number of drug particles per actuation for hypothetical MDI aerosols with MMADs ranging from 1.0 to 5.0 μm and GSDs ranging from 1.3 to 2.0. For all of the calculations, the total drug mass in the aerosol was assumed to be 100 μg per actuation and the particle density was assumed to be 1.3 g/cm^3. The results are plotted graphically in Fig. 1. The number of particles ranged from approximately 2.37 million particles (MMAD=5.0 μm; GSD=1.3) to approximately 1.89 billion particles (MMAD=1.0 μm; GSD=2.0). The results in Fig. 1 can readily be adjusted for MDI aerosols that have a different total drug mass (*M*) since the number of particles is directly proportional to the aerosol mass (Eq. 6). Thus, if the total drug mass per actuation was assumed to be 50 μg, the number of particles would be one half of that shown in Fig. 1 for the equivalently sized aerosol. Whereas the number of particles is linearly proportional to the aerosol mass, it is proportional to the MMAD to the minus third power. Thus increasing the aerosol mass by a factor of two results in a doubling of the number of particles, but decreasing the particle size by a factor of two results in an eightfold increase in the number of particles.

Estimating the Number of Drug Particles Collected in Impactor Testing of MDI Aerosols

Equation 6 can also be used to estimate the number of particles contained in the portion of the MDI plume measured in an MDI size distribution analysis. Previously published Andersen Cascade Impactor (ACI) measurements (11,12) were used to estimate the number of drug particles collected in ACI measurements of several commercial MDIs. The number of particles per actuation for each of these MDIs is summarized in Table I along with the information used in the calculation. The number of particles measured in the ACI per actuation ranged from about 670,000 for Beclovent™ to about 300 million for the two QVAR® MDI products. This large difference was primarily due to the different size distributions of the products. The number of particles calculated was not the total number of drug particles delivered from the MDI valve per actuation since a portion of the aerosol collects in the actuator mouthpiece and USP Induction port used (13). The density of the drug particles was assumed to be approximately 1.3 g/cm^3.

Table II shows the influence of GSD on the number of particles for aerosols with the same MMAD of 2.5 μm, ρ of 1.3 g/cm^3, and *M* of 100 μg/act, but with GSDs ranging from 1.0 (i.e. a monodisperse aerosol) to 2.0. Previous results indicate that the GSD for MDI aerosols is typically between about 1.4 to 2.0 (2). The number of particles varied by a factor of about 8 for aerosols with the same MMAD and total mass due to the influence of GSD. Frequently, in order to estimate the number of drug particles in an MDI plume it is assumed that the aerosol is monodisperse (i.e. GSD=1.0) and simple geometric equations can be used to estimate the number of particles (i.e. Eq. 1 assuming d_m is the monodisperse particle size). However, this results in significant errors for real aerosols that are polydisperse aerosols. Based on Table II, the monodisperse aerosol assumption causes the estimated number of particles to be off by close to a factor of 2 if the GSD is 1.4 and off by about a factor of 8 if the GSD is 2.0. The equations in this paper provide a better means to estimate the number of drug particles in an MDI aerosol.

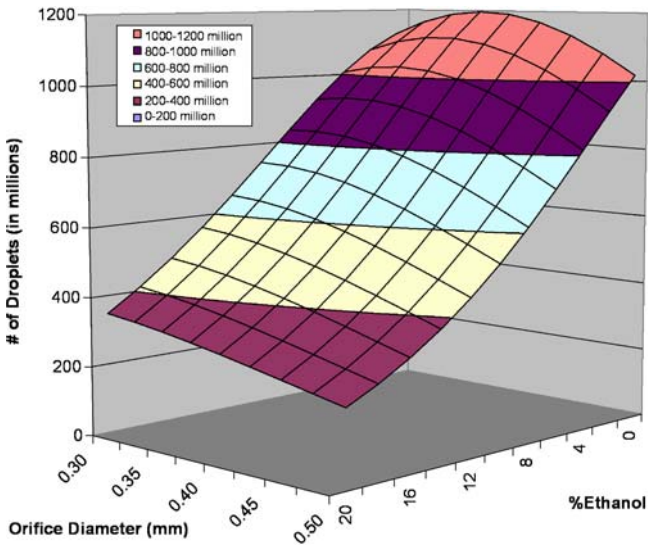

Fig. 2. An estimate of the number of atomized droplets from HFA-134a MDIs with 50 μl valves with varying actuator orifice diameters and ethanol concentrations

Estimating the Number of Atomized Droplets in MDI Plumes

The number of atomized droplets was estimated for a variety of HFA-134a MDI configurations with actuator orifice diameters ranging from 0.3 to 0.5 mm and ethanol concentrations ranging from 0 to 20 percent by weight. As described above, equations developed elsewhere were used to estimate the initial droplet MMD and formulation density and then Eq. 4 was used to estimate the number of atomized droplets. The valve size was assumed to be 50 µl for all of the MDIs. The results are summarized in Fig. 2. The number of atomized droplets ranged from about 220 million to about 1.1 billion droplets per actuation. In general, the number of particles in the MDI plume increased with decreasing ethanol concentration and orifice diameter. However, at the very low ethanol concentrations, there was a peak in the number of particles at orifice diameters between about 0.35 and 0.40 mm. This localized peak is not understood at this point. The results in Fig. 2 can be readily adjusted to estimate the number of particles for HFA-134a MDI configurations with other valve sizes since the number of droplets is directly proportional to *M* which is itself proportional to valve size. Fig. 2 should not be used to estimate the number of droplets for MDIs using HFA-227 or CFC propellants since the empirical equation used to predict the initial droplet size distribution was developed for HFA-134a MDIs.

Relationship of Number of Atomized Droplets and Number of Measured Drug Particles

The number of drug particles measured by the ACI for the two solution MDI products is on the same order of magnitude as the number of atomized droplets. This is not surprising since all of the atomized droplets for a solution MDI contain drug. Thus, the number of drug particles measured in the ACI is equivalent to the number of aerosolized droplets that penetrate through the actuator and USP inlet and into the impactor. This is not true for suspension MDIs since for many of the atomized droplets for suspension MDIs do not contain drug particles. For example, the number of drug particles measured by the ACI for Proventil® HFA (approximately 4.3 million) was more than two orders of magnitude lower than the estimated number of atomized droplets (approximately 540 million). This indicates that most of the atomized droplets do not contain any micronized drug particles. This has important implications related to particle size distribution measurements. In particular, particle sizing techniques, such as time-of-flight or laser diffraction techniques, that are not drug-specific result in the measurement of many particles that do not contain drug. This needs to be considered when interpreting these measurements. However, in many cases, the drug-containing residual particles can be distinguished from those without drug on the basis of size (14).

The two QVAR® aerosols contain roughly the same number of drug particles even though the values of M differ by a factor of 2. These are both solution MDI formulations for which all of the atomized droplets contain drug. Since these two MDIs have nearly identical formulations and hardware, the number of atomized droplets is similar for these two MDI products even though the mass of drug in the droplets varies by a factor of 2. Thus, while these two products generate atomized droplets of nearly the same size distribution, the droplets for the QVAR®80 product have approximately twice as much drug as the droplets for the QVAR®40 product. The result is that the residual particle MMAD for QVAR®80 is larger as described elsewhere (1,2).

CONCLUSIONS

The number of particles in MDI plumes varies by approximately three orders of magnitude among various commercial products and is highly dependent on the MMAD, GSD, and total mass of the aerosol. Calculating the number of particles by assuming that the aerosol is monodisperse and using the MMAD as the particle size leads to an underestimation in the number of particles by as much as a factor of 8. Solution MDIs have more drug particles than suspension MDIs since every atomized droplet contains drug whereas many of the droplets do not contain drug particles for suspension MDIs.

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