

A Correlation Equation for the Mass Median Aerodynamic Diameter of the Aerosol Emitted by Solution Metered Dose Inhalers

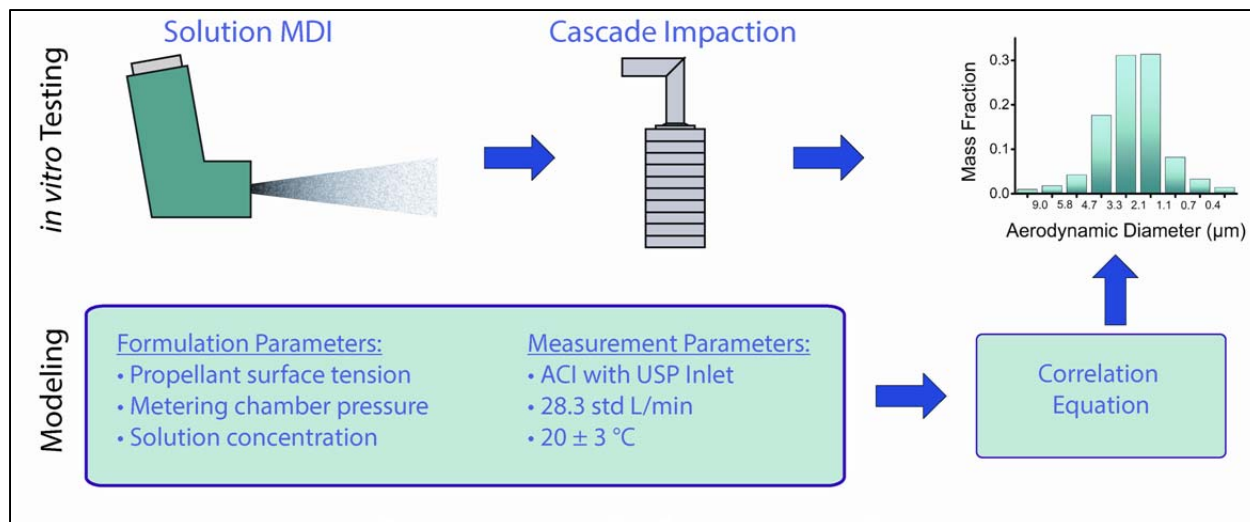
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Abstract:

A correlation equation for the mass median aerodynamic diameter (MMAD) of the aerosol emitted by solution metered dose inhalers (MDIs) is presented. A content equivalent diameter is defined and used to describe aerosols generated by evaporating metered dose inhaler sprays. A large set of cascade impaction data is analyzed, and the MMAD and geometric standard deviation is calculated for each datum. Using dimensional analysis, the mass median content equivalent diameter is correlated with formulation variables. Based on this correlation in combination with mass balance considerations and the definition of the aerodynamic diameter, an equation for prediction of the MMAD of an inhaler given the pressure of the propellant in the metering chamber of the MDI valve and the surface tension of the propellant is derived. The accuracy of the correlation equation is verified by comparison with literature results. The equation is applicable to both HFA (hydrofluoroalkane) propellants 134a and 227ea, with varying levels of co-solvent ethanol.

Keywords: solution metered dose inhaler, mass median aerodynamic diameter, dimensional analysis, droplet diameter distribution, content equivalent diameter

1. Introduction

In spite of its age, the pressurized, metered-dose inhaler (MDI) remains the most popular delivery device for local delivery of drugs to treat respiratory disease. Modern MDI formulations are either suspensions or solutions of drugs and excipients in propellants HFA 134a or 227ea. In cases where the drug has some solubility in the propellant, it is generally preferable to dissolve the drug in the propellant to avoid physical instability (Byron, 1990) or colloidal instability (Brindley, 1999). However, inclusion of a co-solvent is often required to attain sufficient solubility to meet dose targets; ethanol is the most common choice for this purpose (Bell and Newman, 2007; Gupta et al., 2003). General descriptions of the design and principle of operation of the MDI can be found in the literature (da Rocha et al., 2011; Lewis, 2007; Newman, 2005; Smyth, 2003). Figure 1 presents simplified cross-sectional views of an MDI valve prior to and during dose actuation; some key features of the valve are labeled.

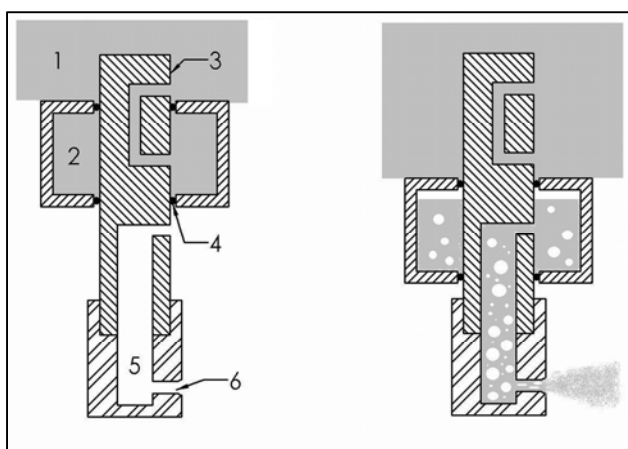


Figure 1: Simplified cross-sectional views of an MDI valve prior to actuation (left) and during actuation (right). 1: bulk solution; 2: metering chamber; 3: valve stem; 4: seals; 5: expansion chamber, sometimes referred to as the actuator sump; 6: actuator orifice.

A factor of critical importance to the efficacy of solution MDIs is the aerodynamic diameter distribution of the drug particles emitted from the device, as a sufficiently fine aerosol must be administered to the patient for efficient lung delivery. It is the aerosol's aerodynamic diameter distribution in combination with its momentum distribution which determines the deposition in the lung (Finlay, 2001). Extensive research has been conducted on the effect of particle size on regional and total deposition in the human lung (Darquenne, 2012; Heyder et al., 1986; Stahlhofen et al., 1989); as a result of this research, MDIs are typically formulated such that most of the drug delivered is in the range of 0.5 – 5 μm aerodynamic diameter (Pilcer and Amighi, 2010).

The final dry particle aerodynamic diameter distribution produced by an MDI is related to the propellant droplet diameter distribution. Therefore it is helpful to consider the atomization mechanisms responsible for droplet formation. The physics involved in converting the bulk solution or suspension into a fine spray in metered dose inhalers are complex. The flow regime is turbulent, the composition is multiphase, the temporal behavior is unsteady and transient, and the entire process takes place in three spatial dimensions

(Finlay 2001). Given the great complexity of the problem, analytical determination of the droplet size distribution in an MDI spray is not currently feasible; therefore, researchers have relied on numerical and empirical methods to study the problem. Clark (Clark, 1992; Clark, 1991) conducted theoretical and experimental investigations into the atomization process from metered dose inhalers containing CFC (chlorofluorocarbon) and HFA propellants, and developed an empirical correlation for the median atomized droplet diameter produced at the actuator orifice for both continuous and metered valve operation. The droplet size was found to depend on the pressure and the vapor quality of the two-phase mixture in the expansion chamber:

$$d_{d,50} = \frac{8.02}{q_{ec}^{0.56} \left(\frac{p_{ec} - p_{\infty}}{p_{\infty}} \right)^{0.46}} \quad (1)$$

where $d_{d,50}$ is the droplet mass median diameter, q_{ec} is the vapor quality (the mass fraction of vapor) of the propellant vapor-liquid mixture in the expansion chamber, p_{ec} is the pressure in the expansion chamber, and p_{∞} is the ambient pressure external to the nozzle. The utility of this correlation is limited because the pressure and quality in the expansion chamber are not typically known *a priori* for a given MDI formulation, though in his thesis Clark suggests that the pressure dependence of this relationship should also hold if the pressure in the metering chamber is used instead of that in the expansion chamber, due to the approximate proportionality between the two. Since the pressure in the metering chamber can be determined theoretically based on the choice of propellant and the amount and type of co-solvent, Equation 1 predicts a decrease in median droplet diameter as the pressure in the metering chamber is increased. Clark concluded, based on the similarity of his droplet diameter correlation to those developed in study of air-blast atomizers, that the atomization mechanism in MDIs was primarily aerodynamic breakup of the liquid phase by the vapor phase. Dunbar et al. conducted numerical (Dunbar and Miller, 1997) and experimental (Dunbar et al., 1997) studies on MDI sprays; Clark's correlation for the droplet size was utilized by Dunbar's numerical model, which gave good agreement with experimental results for droplet size and velocity in the near-nozzle region. However, these researchers concluded, based on flow visualization experiments, that internal flash-boiling, not aerodynamic breakup, was the primary atomization mechanism. A more detailed flow visualization study was performed by Versteeg et al. (Versteeg et al., 2006) utilizing transparent model actuator components, allowing observation of the internal flow in the expansion chamber and nozzle in addition to the external spray. Based on the observations of the internal flow in the model nozzle and the characteristics of the spray issued from the nozzle, they concluded that for the majority of the duration of the metered spray event, flash-boiling was the dominant mechanism of droplet formation.

Despite differing opinions on the underlying mechanism of atomization in MDIs, researchers of solution MDIs have had considerable success employing empirical models to aid in formulation challenges (Lewis et al., 2013). A common technique in some of these studies (Lewis et al., 2004; Stein et al., 2005) is to measure the residual aerodynamic diameter distribution directly and then use this information to infer what has been termed an initial droplet size distribution (Stein and Myrdal, 2004) based on mass balance considerations and the definition of the aerodynamic diameter. Since a significant portion of the propellant vaporizes prior to reaching the actuator orifice, neither the initial concentration

nor the initial droplet diameter can be determined precisely. In this paper we introduce the concept of the content equivalent diameter to formalize what is being measured by such techniques.

2. Materials and methods

2.1. Content Equivalent Diameter

We define the content equivalent diameter, d_c , as the diameter of a sphere that contains the same mass of nonvolatile components, at a volumetric reference concentration, c_r , as the mass of the particle in question. If the mass, m_p , of the particle is known, the content equivalent diameter follows from a mass balance:

$$d_c = \sqrt[3]{\frac{6m_p}{\pi c_r}} = \sqrt[3]{\frac{\rho_p}{c_r}} d_v \quad (2)$$

This concept has been used previously with nebulized aerosols (Roth and Gebhart, 1996). In many cases the mass of an individual particle is not available but rather the particle density, ρ_p , and an analytically accessible equivalent diameter describing the size of the particle can be used. For example, the volume equivalent diameter, d_v , may be used, which yields the second version of Equation (2) above. The volume equivalent diameter includes all open or closed voids in the primary form of the particle (DeCarlo et al., 2004); therefore, the increased volume of porous particles is also accounted for in the particle density.

Alternatively, the particle density can be replaced by the true density of the particle material and the void spaces can be accounted for by incorporating a void fraction into this equation.

Respirable particles are usually characterized by their aerodynamic diameter, which can be assessed by compendial methods. The aerodynamic diameter, d_a , is related to the volume equivalent diameter by (Hinds, 1999)

$$d_a = \sqrt{\frac{\rho_p \zeta}{\rho^* \chi}} d_v, \quad \text{with} \quad \zeta = \frac{C_C(d_v)}{C_C(d_a)} \quad (3)$$

where ρ^* is the reference density (typically 1.00 g / mL), χ is the shape factor accounting for the influence of non-spherical shape on drag force, and ζ captures the effect of non-continuum flow conditions for small particles. The ratio of the Cunningham corrections, C_C , evaluated at the volume equivalent diameter and the aerodynamic diameter, respectively, is very close to 1 and can be neglected if these equivalent diameters are similar. However, for submicron particles with low particle density in air or similar gases under standard conditions, this factor becomes significant and Equation (3) must be solved iteratively, using an appropriate correlation for the Cunningham correction (Allen and Raabe, 1985). The content equivalent diameter can thus be expressed as

$$d_c = \sqrt{\frac{\chi}{\zeta}} \sqrt[3]{\frac{\rho^*}{c_r}} \sqrt[6]{\frac{\rho^*}{\rho_p}} d_a \quad (4)$$

The content equivalent diameter is a property of the aerosol particles and as such, can be defined without detailed knowledge of the actual atomization process.

If the concept of the content equivalent diameter is applied to metered dose inhalers, the volumetric concentration of all non-volatile components in the propellant present in the

canister, c_s , is a useful selection for the reference concentration c_r . The concentration c_s is accurately set during the fill finish process of the inhaler. Thus, using Equation (4) we can relate the aerodynamic diameter of the aerosol from a metered dose inhaler to its content equivalent diameter:

$$d_a = \sqrt{\frac{\zeta}{\chi}} \sqrt[3]{\frac{c_s}{\rho^*}} \sqrt[6]{\frac{\rho_p}{\rho^*}} d_c \approx \sqrt[3]{\frac{c_s}{\rho^*}} \sqrt[6]{\frac{\rho_p}{\rho^*}} d_c \quad (5)$$

Because most metered dose inhalers produce aerosols with a mass median aerodynamic diameter larger than 1 μm (Mitchell et al., 2003) with aspect ratios expected to be close to 1 (Grainger et al., 2012; Lewis et al., 2013), non-continuum and shape effects can usually be neglected. The effect of varying particle density is also quite small for typical pharmaceutical actives or excipients, due to the weak sixth root dependence in Equation (5). Hence, an approximate estimate of particle density, if available, may be used.

Utilizing Equation (5) in combination with a means of measuring the aerodynamic diameter distribution of the aerosol from MDIs allows us to study the effects of device and formulation variables on the content equivalent diameter distribution. We use this approach to develop a single correlation for the MMAD of solution MDIs as measured by cascade impaction operating at laboratory conditions, accounting both for choice of propellant (134a or 227ea) and for ethanol concentration.

2.2. Cascade impaction testing of metered dose inhalers

Cascade impaction testing on 170 solution MDIs was performed; the results comprise the data set used to develop the model presented below. MDIs consisted of an active pharmaceutical ingredient dissolved in either propellant HFA 134a or HFA 227ea using ethanol as a co-solvent; in some cases glycerol was added as a non-volatile modulator of aerodynamic size distribution. All MDIs were filled using a two-stage filling process: first, known quantities of drug, ethanol, and non-volatile additive were added and a valve was crimped onto the canister; then propellant was filled through the valve. Filled MDIs were then paired with an actuator prior to testing. Valves and actuators were supplied by Bepak (Bepak Ltd., King's Lynn, UK). Formulation and device variable ranges of the tested MDIs appear in Table 1.

Aerodynamic diameter distributions were measured with an Andersen cascade impactor (Mark II, Copley Scientific, Nottingham, UK) fitted with a USP (United States Pharmacopeia) induction port (Apparatus 1, USP 35) and comprising eight metal stages plus a final filter. All measurements were performed at laboratory conditions of 20 ± 3 °C at ambient humidity. Air flow rate through the impactor was 28.3 ± 0.5 standard L/min for all tests. Metered dose inhalers were actuated from one to ten times per determination depending on active ingredient and dose. The mass of drug deposited on each impactor plate was determined via high-performance liquid chromatography or ultra-performance liquid chromatography, with method dependent on active ingredient.

Variable	Tested range (X – Y) or discrete values (X, Y, ..., Z)
Active pharmaceutical ingredient	b-oestradiol 17-enanthate, beclomethasone dipropionate, budesonide, dex budesonide, diisobutyl apomorphine, flunisolide, formoterol fumarate, ipratropium bromide, oestradiol valerate, tetrahydrocannabinol hemisuccinate
Valve metering volume (μL)	25, 50, 100
Actuator orifice diameter (mm)	0.22, 0.30, 0.42
Propellant type	HFA 134a, HFA 227ea
Drug dose, metered (μg)	6 – 1000
Total solution concentration [drug + non-volatile additive, if used] (mg/mL)	0.4 – 22.0
% Ethanol (w/w)	2.0 – 15.2

Table 1: Summary of the ranges of the device and formulation variables in the cascade impaction data set used to develop the correlation.

All aerodynamic diameter distributions were assumed to be log-normal. The cumulative mass aerodynamic diameter distribution from each cascade impaction measurement was fit using the best-fit log-normal cumulative distribution function (Hinds, 1999) with mass median aerodynamic diameter and geometric standard deviation as the fitting parameters in a nonlinear least squares analysis.

2.3. Dimensional analysis

The method of Buckingham (Buckingham, 1914) was used to simplify the analysis of the cascade impaction data. Dimensional analysis is described procedurally elsewhere (Kundu et al., 2012). As the objective of the analysis was to find a correlation for the mass median content equivalent diameter at the formulated solution concentration, $d_{c,50}$, independent formulation and device variables expected to have an effect on $d_{c,50}$ were selected assuming that flash boiling and aerodynamic breakup contribute to the atomization process; they are summarized in Table 2.

Since the only variables containing units of temperature were c_p and $(T_0 - T_e)$, they were grouped as a product, $c_p(T_0 - T_e)$, to limit the number of dimensionless groups required. Including $d_{c,50}$ there were then six variables involved in the system, which contains three independent dimensions (mass, length, time); consequently three independent dimensionless groups describe this system.

Variable	Symbol	Reasons for inclusion in analysis
Mass median content equivalent diameter	$d_{c,50}$	Dependent variable of interest
Pressure in MDI metering chamber	p_{mc}	Primary source of energy for atomization
Actuator orifice diameter	d_o	Non-dimensionalization of $d_{c,50}$
Surface tension of liquid propellant in air	σ_{pa}	Related to the surface energy of the propellant droplets upon atomization
Specific heat capacity of liquid propellant	c_p	Describes thermal energy in the liquid propellant; relevant to flash atomization
Temperature drop of propellant during atomization	$(T_0 - T_e)$	Describes exchange of sensible heat for latent heat during propellant evaporation; relevant to flash atomization
Specific enthalpy change of vaporization of propellant	ΔH_v	Related to the amount of energy consumed to evaporate propellant; relevant to flash atomization

Table 2: Summary of the variables in the dimensional analysis, and a brief explanation for the inclusion of each.

Using d_o , σ_{pa} , and ΔH_v as repeating variables and forming the dimensionless groups, the following relationship was obtained:

$$\Pi_1 = \frac{d_{c,50}}{d_o} = f(\Pi_2, \Pi_3) \quad (6a)$$

with

$$\Pi_2 = \frac{p_{mc} d_o}{\sigma_{pa}} \quad (6b)$$

$$\Pi_3 = \frac{c_p (T_0 - T_e)}{\Delta H_v} \quad (6c)$$

where f denotes a functional relationship to be determined (i.e. the desired correlation).

Π_2 as defined by Equation (6b) resembles the Weber number,

$$We_L = \frac{\rho_L V_L^2 d_o}{\sigma_{LG}}$$

where ρ_L refers to the liquid density, V_L to the liquid velocity relative to the surrounding medium, and σ_{LG} is the surface tension of the liquid in the surrounding medium. The Weber number arises in the study of liquid jet stability and atomization (Bayvel and Orzechowski, 1993). Assuming a dynamic pressure scaling relationship,

$$p_{mc} \approx \rho V^2,$$

the similarity between Π_2 and the Weber number is apparent. In the context of MDIs, density and velocity are difficult to measure due to the two-phase nature of the flow at the actuator orifice exit. However, as will be seen below, the metering chamber pressure p_{mc} is more readily specified. Thus Π_2 provides an easily calculated surrogate for the Weber number, encompassing the effects of jet inertia and droplet surface energy.

Π_3 as defined by Equation (6c) is similar to the Jakob number,

$$Ja = \frac{\rho_l c_p (T_0 - T_e)}{\rho_v \Delta H_v}$$

where ρ_l and ρ_v are the liquid and vapor phase densities, respectively. The Jakob number occurs in theoretical and experimental investigations of bubble growth rate in flashing atomization (Kitamura et al., 1986; Sher et al., 2008).

2.4. Calculation of dimensionless groups

To calculate the mass median content equivalent diameter for each MDI, Equation (5) was adapted using some simplifying assumptions. Assuming spherical particles with particle density equal to the reference density and neglecting non-continuum effects, the mass median content equivalent diameter can be expressed as a function of the measured MMAD:

$$d_{c,50} = \sqrt[3]{\frac{\rho^*}{c_s}} MMAD \quad (7)$$

When using Equation (7) to analyze a set of impaction data, it is important that conditions which may affect the rates of evaporation or growth (i.e., gas temperature, flow rate, and relative humidity) are held relatively constant across the measurements.

Examining Equations (6a-6c), some physical properties of the propellant system must be known in order to calculate values for the dimensionless groups. As all of the tested solution MDIs were dilute, with an initial concentration of non-volatile components of at most 22 mg/mL, they were approximated as pure propellant-ethanol mixtures for the purposes of evaluating physical properties. References for the physical properties and the equations utilized in this model are given in the Appendix.

The metering chamber pressure p_{mc} was equated to the vapor pressure of the HFA-ethanol mixtures. Published data for the vapor pressure of HFA-ethanol mixtures at 20 °C were used; see the Appendix. The data from 0 to 30% ethanol by weight were adequately approximated with a linear fit. This approach was taken since due to the non-ideal behavior of the HFA-ethanol mixtures, use of Raoult's Law for the calculation of vapor pressure results in significant errors (Smyth et al., 2002; Vervaet and Byron, 1999).

To calculate the temperature dependent material properties σ_{pa} , c_p , ΔH_v and the temperature drop during atomization ($T_0 - T_e$), it was necessary to estimate the final temperature of the propellant droplets upon complete atomization, T_e . Liquid phase breakup and droplet formation were assumed to occur during flash-boiling of propellant, with atomization ceasing once flash-boiling stops. Therefore the boiling temperature of the propellant-ethanol mixture was chosen instead of the droplet wet bulb temperature as the more relevant temperature to the phenomena being modeled, and T_e was assumed to be the

normal boiling point of the propellant only. The relatively small boiling point increase due to the presence of ethanol was neglected.

With an approximate final temperature T_e determined, a reference temperature for the calculation of material properties was defined:

$$\bar{T} = \frac{(T_0 + T_e)}{2} \quad (8)$$

Surface tension, specific heat capacity, and specific enthalpy change of vaporization for each MDI were then calculated using the relationship

$$\varphi_m = Y_p \varphi_p(\bar{T}) + Y_e \varphi_e(\bar{T}) \quad (9)$$

where φ_m denotes the mass-weighted material property of the mixture, Y_p and Y_e are the mass fractions of propellant and ethanol, respectively, and φ_p and φ_e are the pure component property at \bar{T} for propellant and ethanol, respectively. Equations for calculating the pure component physical properties are presented in the Appendix.

Once all of the variables in Table 2 were determined for each observation in the data set, the dimensionless groups of Equations (6a-6c) were calculated, and the data were evaluated to find a correlation for the dimensionless mass median content equivalent diameter as a function of the independent dimensionless groups.

3. Results and Discussion

The range of values of the dimensionless groups for the evaluated cascade impaction data are summarized in Table 3. Since the dimensionless group Π_3 did not vary much in the data set, it could not be assessed if a correlation with Π_1 existed. Thus for the purposes of the model presented here, Π_1 was considered to be independent of Π_3 . In contrast, a clear relationship between Π_1 and Π_2 can be seen in Figure 2. The best fit power function yielded an exponent of -1.01, so for simplicity the data were re-fit with an exponent of -1 with no decrease in coefficient of determination (R^2) value:

$$\Pi_1 = 416 \Pi_2^{-1}, \quad R^2 = 0.75 \quad (10)$$

The R^2 value of 0.75 indicates appreciable unexplained variation in the data, which is unsurprising given the simplicity of the model. However, the relatively good fit identifies the primary variables influencing the mass median content equivalent diameter, while some of the unexplained variation is likely attributable to variables that were not considered in this analysis.

Dimensionless group	Mean \pm Standard Deviation	Relative Standard Deviation
Π_1	0.0398 \pm 0.0079	20%
Π_2	10,800 \pm 2160	20%
Π_3	0.118 \pm 0.010	8%

Table 3: Mean, standard deviation, and relative standard deviation of the values of the three dimensionless groups for the cascade impaction data set.

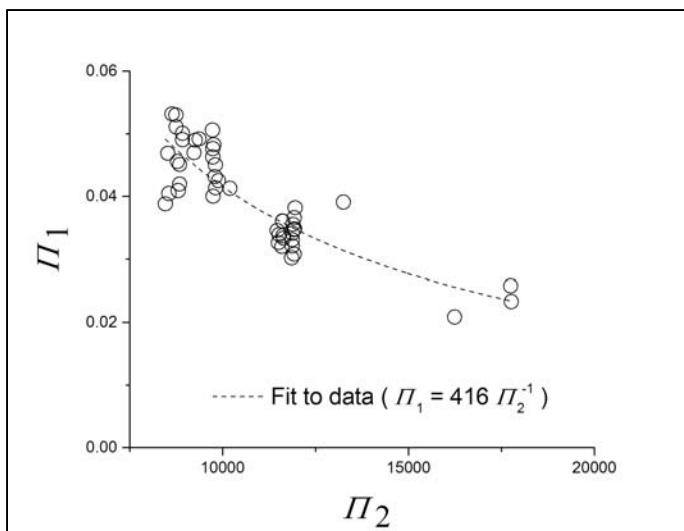


Figure 2: Plot of Π_1 vs. Π_2 and a power-law curve fit to the data.

Inserting the definitions of Π_1 and Π_2 from Equations 6a and 6b into the fitted function, and solving for the mass median content equivalent diameter yields

$$d_{c,50} = \frac{416\sigma_{pa}}{p_{mc}}, \quad (11)$$

from which we find a dependence of $d_{c,50}$ on propellant surface tension in air and metering chamber pressure only. Actuator orifice diameter d_o has cancelled out, consistent with other researchers' findings that for solution MDIs, actuator orifice diameter has little effect on content equivalent diameter distribution (Lewis et al., 2006; Stein and Myrdal, 2004).

Substituting Equation (11) into Equation (7) and solving for MMAD yields

$$MMAD = 416 \sqrt[3]{\frac{c_s}{\rho^*} \frac{\sigma_{pa}}{p_{mc}}} \quad (12),$$

Equation (12) is valid for any consistent set of units, and gives the MMAD in meters if the independent variables are specified in SI units. It is a correlation equation that predicts the mass median aerodynamic diameter of a solution MDI given the formulated concentration of drug plus non-volatile excipient, the surface tension of the propellant in air, and the metering chamber pressure. Since the correlation was developed using the concept of the content equivalent diameter, which is a parameter of the measured aerosol, it is only strictly valid for similarly measured aerosols, i.e., for cascade impaction data generated in a 20 °C laboratory, with air flow rate of 28.3 standard L/min, and using a USP throat inlet. These are relevant conditions for MDI development. Use of this correlation at other conditions should be considered extrapolation and the results treated with due caution; as other research (Stein and Myrdal, 2004) has demonstrated, such correlations are specific to the means of sampling and measuring the aerosol.

To test the accuracy of the correlation of Equation (12), it was applied to experimental data in the literature and the predicted MMAD was compared to the experimentally determined values; see Figure 3. Meakin et al. (Meakin et al., 2000) tested solution MDIs with both HFA 134a and 227ea as propellant with an Andersen cascade impactor, as was done in this work. Myrdal et al. (Myrdal et al., 2004) and Stein and Myrdal (Stein and Myrdal, 2004) measured the aerodynamic diameter distributions of solution MDIs in both

propellants, using a time-of-flight aerodynamic particle sizer (APS) equipped with a USP inlet; in Myrdal's work, a 20 cm extension was added downstream of the USP inlet and prior to the sizing equipment.

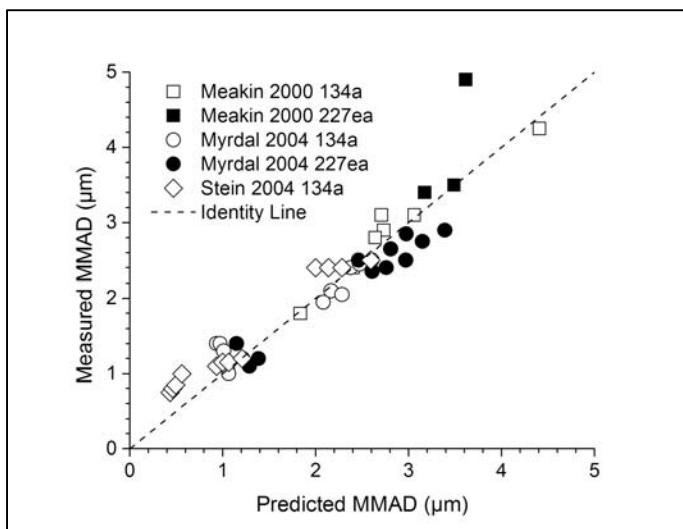


Figure 3: Comparison of predicted vs. measured MMAD of experimental data from a variety of literature sources. The data of Meakin (squares, (Meakin et al., 2000)) were generated using an Andersen cascade impactor. The data of Myrdal (circles, (Myrdal et al., 2004)) were generated using a time-of-flight aerodynamic particle sizer (APS) equipped with a USP inlet plus inlet extension. The data of Stein (diamonds, (Stein and Myrdal, 2004)) were also generated with an APS, with a USP inlet and no extension. Open symbols: propellant 134a + ethanol; closed symbols: propellant 227ea + ethanol.

Our correlation predicts the data of Meakin et al. quite well, save for one outlier. It also predicts the data measured with the APS with reasonable accuracy, showing that some extrapolation is possible. Overall Equation (12) predicts this sample of literature data adequately given the different techniques employed by each source. While prior research has yielded similar correlation equations (Lewis et al., 2004; Stein and Myrdal, 2004), these have been propellant-specific, requiring a separate equation for each propellant.

The calculated GSDs of the measured aerodynamic diameter distributions of the entire dataset ranged from 1.8 to 3.1, with an overall average value of 2.1. As no correlations with the dimensionless groups or independent variables were found, use of the overall average value of 2.1 for the GSD is recommended for predictive purposes.

4. Conclusions

The content equivalent diameter distribution, as defined here, is a property of the measured residual aerosol. For MDIs, use of the content equivalent diameter distribution allows experimental investigation of the effects of formulation and device variables on the residual aerosol size distribution without necessitating a detailed description of the droplet diameter or momentum distribution of the propellant spray.

Dimensional analysis was utilized to identify dimensionless groups describing the mass median content equivalent diameter of the portion of the spray sized in a standard cascade impaction testing apparatus. Dimensionless mass median content equivalent diameter was found to be correlated with one dimensionless group; using this result, a correlation for the MMAD of the resulting aerosol was developed, depending on propellant vapor pressure in the metering chamber, surface tension of the liquid propellant in air, and the formulated concentration of non-volatiles in the HFA solution. Unlike propellant-specific correlations previously presented in the literature, the correlation developed here links the observed behavior to physical properties of the system, offering the potential to describe novel or unconventional propellant-co-solvent combinations. The equation is simple and provides the formulator of solution MDIs with a tool to easily select an appropriate level of non-volatile additives to achieve a target MMAD for a given drug formulation. It is valid for cascade impaction testing of solution metered dose inhalers provided that the testing parameters are within the ranges described in section 2.2.

Appendix: Physical Properties of Propellant-Ethanol Mixtures

Metering chamber pressure p_{mc} was equated to the vapor pressure of the HFA-ethanol mixture at 20 °C. Linear fits to vapor pressure data from a propellant supplier (Solvay Fluor GmbH, 2007) in the range of 0 – 30 % by weight ethanol were used. The fitting equations are

$$\begin{aligned} p_{134a+EtOH} &= 5.72 \times 10^5 - 2.8 \times 10^5 X_{EtOH} \\ p_{227ea+EtOH} &= 3.90 \times 10^5 - 2.7 \times 10^5 X_{EtOH} \end{aligned}$$

where $p_{134a+EtOH}$ and $p_{227ea+EtOH}$ are the absolute vapor pressure of HFA 134a or HFA 227ea mixed with ethanol in Pa, and X_{EtOH} is the mass fraction of ethanol present in the mixture.

Surface tension in air, specific heat capacity, and specific enthalpy of vaporization for propellant-ethanol mixtures were evaluated using mass weighting per Equation (9), with pure component properties evaluated at the mean temperature defined in Equation (8). The equations used to approximate the pure component properties are summarized in Table 4.

Property	Equation	Reference
Surface tension in air in N/m; T in K	$\sigma_{134a} = 0.06021747 \left(1 - \frac{T}{374.2}\right)^{1.26}$	(Mexichem UK Limited, 2010a)
	$\sigma_{227ea} = 0.05047773 \left(1 - \frac{T}{376.0}\right)^{1.26}$	(Mexichem UK Limited, 2010b)
	$\sigma_{EtOH} = 0.05 \left(1 - \frac{T}{513.9}\right)^{0.952}$	(Mulero et al., 2012)
Specific heat capacity at constant pressure in J/kg K; T in K	$c_{p,134a} = -132,323 + 1,000.153 T - 2.8 T^2 + 2.79 \times 10^{-3} T^3 + \frac{9.396558 \times 10^8}{T^2}$	(Mexichem UK Limited, 2010a)
	$c_{p,227ea} = -139,133 + 1,001.004 T - 2.68 T^2 + 2.55 \times 10^{-3} T^3 + \frac{1.088237 \times 10^9}{T^2}$	(Mexichem UK Limited, 2010b)
	$c_{p,EtOH} = 2770 - 14.91 T + 0.09132 T^2 - 2.574 \times 10^{-4} T^3 + 3.564 \times 10^{-7} T^4$	(Brown Jr and Ziegler, 1979)
Enthalpy change of vaporization in J/kg; T in K	$\Delta H_{v,134a} = 163,731.3 x + 534,468.4 x^2 - 510,952 x^3 + 219,188.6 x^4$ with $x = \sqrt[3]{1 - \left(\frac{T}{T_c}\right)}$ and $T_c = 374.2$ K	(Mexichem UK Limited, 2010a)
	$\Delta H_{v,227ea} = 39,210.01 x + 850,109 x^2 - 1,725,330 x^3 + 1,188,758 x^4$ with $x = \sqrt[3]{1 - \left(\frac{T}{T_c}\right)}$ and $T_c = 376.0$ K	(Mexichem UK Limited, 2010b)
	$\Delta H_{v,EtOH} = 1,094,677 \exp(0.4775 T_r)(1 - T_r)^{0.4989}$ with $T_r = \frac{T}{513.9 \text{ K}}$	(NIST Chemistry Webbook, 2011)

Table 4: The equations used to approximate physical properties of ethanol and propellants HFA 134a and HFA 227ea.

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