International Journal of Pharmaceutics 422 (2012) 101–115

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

A model for predicting size distributions delivered from pMDIs with suspended drug

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ARTICLE INFO

Article history:
Received 30 June 2011
Received in revised form 11 October 2011
Accepted 18 October 2011
Available online 21 October 2011

Keywords:
Aerodynamic particle size
Pressurized metered dose inhaler (pMDI)
Simulation model
Suspension formulation

ABSTRACT

A new model has been developed for predicting size distributions delivered from pressurized metered dose inhalers (pMDIs) that contain suspended drug particles. This model enables the residual particle size distribution to be predicted for a broad range of formulations. It expands on previous models by allowing for polydisperse micronized input drug, multiple suspended drugs, dissolved drug, and dissolved or suspended excipient to be included in the formulation. The model indicates that for most pMDI configurations, the majority of droplets contain no drug or a single drug particle and the residual particle size distribution delivered from the pMDI is essentially equivalent to the size distribution of the micronized drug used in the formulation. However, for pMDIs with a high drug concentration or that use small micronized drug particles, there can be a substantial fraction of the droplets that contain multiple drug particles. The residual particle size distribution obtained from these pMDIs can be substantially larger than the size distribution of the micronized drug. Excellent agreement was observed between size distributions predicted using this model and those obtained from experimental cascade impactor measurements ($r^2 = 0.97$), thus demonstrating the ability of the model to accurately predict the size distributions obtained from suspension pMDIs.

1. Introduction

1.1. Background

For over half a century pressurized metered dose inhalers (pMDIs) have been widely used in treatments for lung diseases such as asthma and chronic obstructive pulmonary disease. More recently, the utility of pMDIs has been investigated for the treatment of lung cancer and for systemic delivery of insulin and other peptides (Fulzele et al., 2006; Kapitza et al., 2003; Myrdal et al., 2004; Zheng et al., 2001). Pressurized MDIs use propellants to atomize precise amounts of formulation into droplets that are capable of being delivered to the lung. The chlorofluorocarbon (CFC) propellants used in early pMDIs have been replaced by non-ozone depleting hydrofluoroalkane (HFA) propellants (Ross and Gabrio, 1999; Atkins, 1999; Leach, 2005). The drug contained in the formulation can be dissolved in the formulation, producing a solution, or can be dispersed in the formulation, producing a suspension. In addition to a high pressure propellant and drug, pMDI formulations may also contain cosolvents, such as ethanol, or other excipients. These excipients may be surfactants, polymers or micronized excipients that may function in providing physical stability to a suspension formulation, modifying the size of residual drug particles, or providing sustained drug release (Brambilla et al., 1999 Jinks, 2003; Leach et al., 2000; Louey and Garcia-Contreras, 2004).

The ability of a pMDI to deliver drug to the lung is largely dependent on the residual aerodynamic particle sizes of the atomized droplets. The particle sizes of pMDI aerosols are often lognormally distributed, thus the aerodynamic particle size distribution (APSD) of the aerosolized particles can be described using the mass median diameter (MMD) or mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). Generally, particles less than approximately 5 μm MMAD are capable of penetrating into the lung with smaller particles having the best chance to penetrate into the deep lung (Labiris and Dolovich, 2003). The ideal aerodynamic particle size for delivery of drugs to the lung is subject to much debate and depends on the desired location in the respiratory tract for delivery of the particular drug (Hickey et al., 1996; Harrison et al., 1997; Howarth, 2001).

For solution pMDIs, the size of residual particles delivered to the patient is a function of the initial droplet size and the concentration of non-volatile components (i.e. drug and/or excipient) in the formulation (Brambilla et al., 1999; Stein and Myrdal, 2004). During the actuation of the device, the high pressure propellant acts

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doi:10.1016/j.ijpharm.2011.10.035

as an energy source to dispense the formulation from the device and atomize the formulation into a polydisperse distribution of small droplets. The atomized droplet size distribution is lognormal in nature and generally has a GSD of approximately 1.6–1.8 (Stein and Myrdal, 2004). The initial MMD of the atomized droplets vary in size depending on the propellant, cosolvent, valve size, and actuator orifice diameter but is typically around 8–12 μm for HFA-134a-based pMDIs (Stein and Myrdal, 2004). Once atomized, these initial droplets undergo rapid evaporation of the propellant and cosolvent, if present. After the evaporation is completed, the residual particles from a solution pMDI are nearly spherical and contain drug and any non-volatile excipient present in the formulation (McKenzie and Oliver, 2000; Stein and Myrdal, 2004). Since the drug is dissolved in a homogenous solution prior to atomization, the size of each residual particle is proportional to the initial size of its respective atomized droplet. Thus, larger initial droplets result in larger residual particles and smaller initial droplets result in smaller residual particles.

The formation of the residual particles from suspension pMDIs is more complex than from solution pMDIs and is illustrated in Fig. 1. As is the case with solution pMDIs, the suspension formulation is atomized into droplets with a range of initial droplet diameters which depends on the formulation and device. The initial droplets contain propellant, cosolvent, any dissolved non-volatile excipients (e.g. surfactant), and varying number of suspended drug particles. The formulation can also contain dissolved drug, but this is not typical. Some droplets contain no drug particles, as depicted by droplets A and B in Fig. 1, while others contain 1, 2, or even more drug particles as depicted by droplets C to E in Fig. 1. The number of drug particles contained within the droplets depends on the size of the micronized drug, the concentration of the drug in the formulation, and the size of the initial droplet. The aerodynamic size of the residual particles depends on the number of suspended drug particles contained in a given droplet, the size of these suspended drug particles, the shape of the residual particle, and the mass of non-volatile components contained in the droplet. The shape of the residual particles with greater than one drug particle can deviate from a perfect sphere, as presented by the residual particle in Fig. 1C. The shape factor and packing density, discussed in Section 2.1.6, allow for calculation of the aerodynamic diameter for these residual particles. The likelihood of any given droplet having one or more drug particles depends on the size of the atomized droplet and on the formulation and increases as the number of drug particles present per unit volume of formulation and the droplet volume increase.

The atomization of nebulized monodisperse suspensions was previously described by Raabe (1968). In order to develop good calibration aerosols, Raabe developed an equation to estimate the amount of dilution of a formulation of monodisperse polystyrene latex (PSL) particles is required in order to minimize the number of "multiplets" (i.e. residual particles containing more than one PSL particle). The delivery from suspension pMDIs has been modeled by Gonda (1985) and Chan and Gonda (1988) who built upon the work of Raabe to model delivery of monodisperse particles contained in polydisperse droplets. In reality, however, the delivery of drug from suspension pMDIs is more complicated than that modeled by Gonda since the drug particles are virtually always polydisperse and most suspension pMDIs include non-volatile excipients that change the aerodynamic size of the residual particles.

1.2. Characterizing the size distribution of the initial droplets

One of the challenges in modeling both solution and suspension pMDI drug delivery is determining the size distribution of the initial droplet diameters. This is a critical input for predicting the residual aerosol size distribution delivered from either solution or suspension pMDIs. The initial droplet size distribution can be estimated theoretically, experimentally, or empirically through equations. Theoretical models have been developed for predicting the size distribution of droplets atomized from pMDIs using droplet breakup models (Shi and Kleinstreuer, 2007). However, these models are computationally intensive and the ability of these models to accurately predict initial droplet sizes for highly volatile liquids such as propellants has not yet been demonstrated.

Experimental measurement of the initial droplet distribution is also very challenging as a result of the extremely rapid changes in droplet size immediately after atomization due to evaporation of the highly volatile formulation. Phase-doppler particle anemometry (PDPA) has been shown to provide useful insight into the size of the atomized droplets (Dunbar, 1997; Dunbar et al., 1997), but requires a high level of expertise to generate and analyze the data. Additional challenges include the small measurement volume for the technique and the challenge of measuring near to the exit of the actuator nozzle. Laser diffraction is another approach for experimentally characterizing droplet size distributions. In addition to the technical challenges described for the PDPA technique, laser diffraction has the challenge of beam steering caused by changes in the index of refraction of the air due to the high concentration of propellant vapor in the plume (Smyth and Hickey, 2003). Thus, while experimental approaches provide useful insight, they are limited in their ability to characterize the size distribution of the droplets just after atomization.

Another approach for determining the size distribution of initial droplets is to use theoretical equations describing the relationship between the size of the initial droplets and residual particles. For solution pMDIs, it is possible to estimate the initial droplet size distribution by measuring the size distribution of the residual particles after all of the volatile components of the formulation evaporate and then theoretically calculating the initial droplet sizes using Eq. (1) (Stein and Myrdal, 2004). The MMD of the initial droplets (MMD_I) from a solution formulation can be readily predicted based on knowledge of the residual particle mass median diameter (MMD_R) and properties of the formulation – particularly the concentration of the non-volatile components (C_{NV}, weight fraction) of the formulation – as described by Eq. (1).

$$MMD_I = MMD_R \times \left(\frac{\rho_I C_{NV}}{\rho_R}\right)^{-1/3} \quad (1)$$

where ρ_I and ρ_R are the densities of the initial droplets and the residual particles, respectively. The ρ_I is the same as the density of the formulation, ρ_{form}. The GSD of the initial droplet distribution (GSD_I) and the residual particle distribution (GSD_R) is the same (Stein and Myrdal, 2004). An advantage of this approach is that it relies on measurement of the residual aerosol size distribution. The residual size distribution is much easier to measure than the initial droplet size distribution since the size is no longer changing when measured.

Previous research has been used to provide an empirical equation for predicting the initial droplet size distribution for 1,1,1,2-tetrafluoroethane (HFA-134a) solution pMDIs as a function of the ethanol concentration, the valve size, and the actuator orifice diameter as presented in Eq. (2) (Stein and Myrdal, 2004).

$$MMD_I = 6.90 + 0.0441 \times VS + 23.6 \times C_{EtOH} - 63.8 \times C_{EtOH}^2 + 24.7 \times C_{EtOH} \times OD - 0.129 \times C_{EtOH} \times VS \quad (2)$$

where MMD_I is in μm, VS is the valve size (μL), C_{EtOH} is the concentration of ethanol in the formulation (weight fraction), and OD is the actuator orifice diameter (mm). Eq. (2) has been shown to provide accurate size distribution estimates for HFA-134a solution pMDIs for a variety of formulations, valves, and actuator configurations

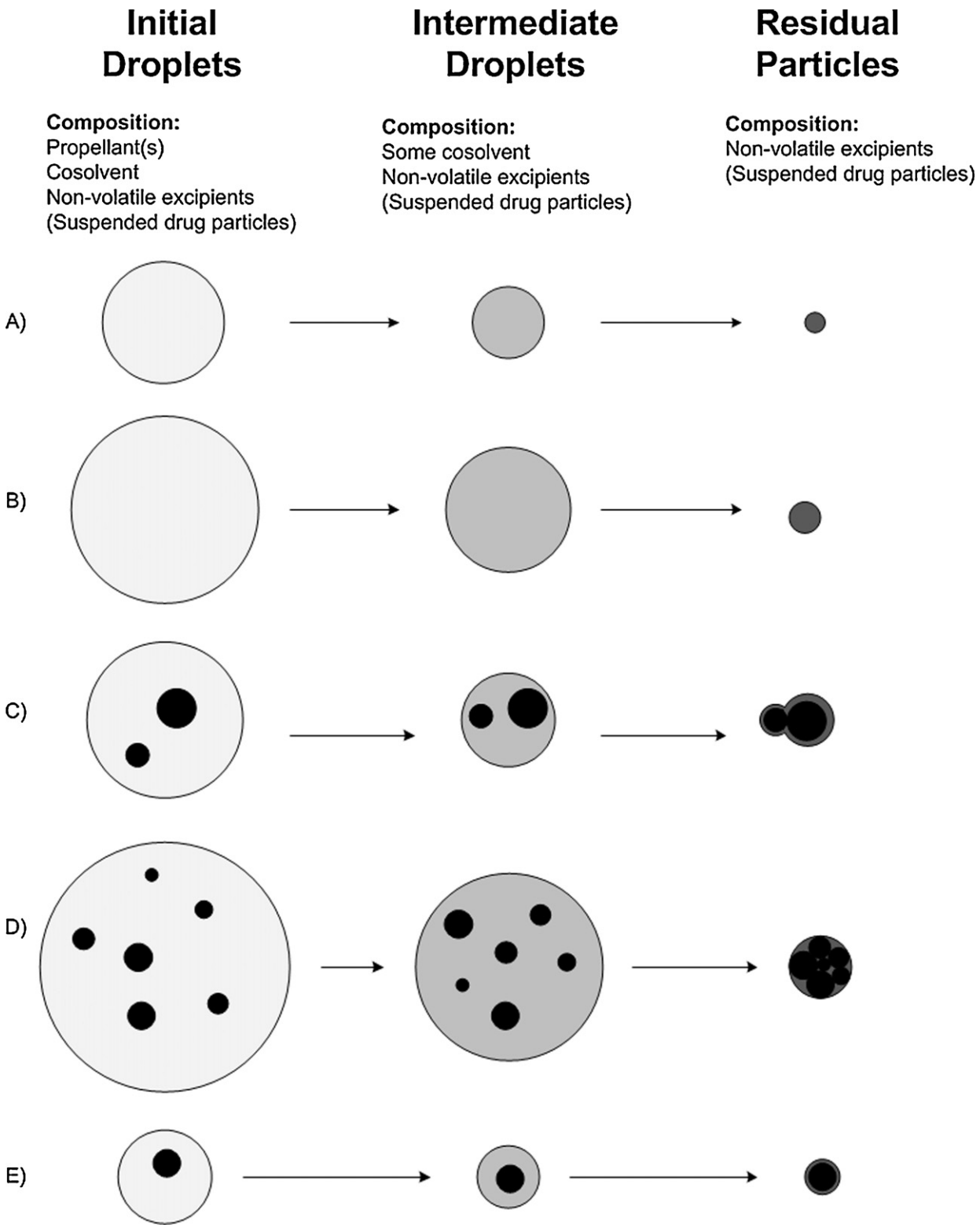

Fig. 1. Depiction of droplet atomization process from suspension pMDIs. Some droplets, can contain no drug particles, as depicted in A and B, while others can contain 1, 2, or more drug particles as depicted in C to E. The size of the residual particles depends on the size and number of drug particles contained within the droplet and the concentration of any non-volatile excipient (usually surfactant) dissolved in the formulation.

(Stein and Myrdal, 2004). It is not possible to generate a separate empirical equation for the initial droplet size distribution for suspension pMDIs since the presence of varying number of drug particles in each residual particle precludes the use of simple equations such as Eq. (1).

1.3. Purpose

The objective of this research is to expand on the work of Raabe and Gonda to develop a computational model to describe the residual aerosol delivered from suspension pMDIs taking into account

the polydispersity of the raw drug particles and atomized droplets and the inclusion of non-volatile excipients in the formulation (Raabe, 1968; Gonda, 1985; Chan and Gonda, 1988). This paper will apply the developed model to theoretically predict the residual particle size distribution from suspension pMDI formulations and the results will be compared to experimental measurements.

2. Materials and methods

2.1. Description of theoretical model

Fig. 2 represents the algorithm that is used in this research to determine the residual particle size distribution delivered from pMDIs. The algorithm requires detailed formulation information, such as weight concentration (% w/w) of each component, the density of each component (g/cm^3), and the APSD of the raw micronized drug. In addition, the initial droplet size distribution must be provided. Once the formulation information is provided and the initial droplet size distribution is determined, Steps 1–5 in Fig. 2 are used to predict, on a droplet-by-droplet basis, the size and composition of residual particles that results from each atomized droplet.

For each droplet to be modeled, the first step in the algorithm is to determine the initial droplet size. Since the overall distribution of atomized droplets is one of the inputs to the model, the size of any given atomized droplet must be determined by randomly sampling from the overall initial droplet size distribution. This "random sampling" is done by using a random number generator to generate a number between 0 and 1 and then finding the droplet size for the inverse cumulative distribution function that corresponds to this random number. Subsequently, the number of drug particles contained in the droplet can be determined. The Poisson statistical distribution is used to determine the probabilities of the droplet containing 0, 1, 2, 3, etc., suspended drug particles. Once these probabilities are calculated, the number of suspended drug particles contained in the droplet is determined by randomly sampling from the Poisson distribution in a manner similar to that used to sample the initial droplet diameter. After the number of drug particles in the droplet is known, the sizes of these drug particles are determined (Step 3) by a similar random sampling from the inverse cumulative distribution function of the micronized drug which is known since the size distribution of the micronized drug is one of the inputs to the algorithm. If any dissolved drug or excipient is included in the formulation, the mass and volume of these are determined (Step 4) using simple calculations and the formulation information provided in the input stage. In Step 5, the aerodynamic diameter of the residual particle is calculated based on the mass and volume of drug and/or excipient determined in Step 4 and based on an estimation of the shape factor which is based on the number of drug particles contained in the residual particle. The content of volatiles in the formulation (i.e. propellant and co-solvent) do not contribute to the size distribution of the residual particles, since it is assumed that the residual particles are "dry" and only contain dissolved and/or suspended non-volatiles that were simulated in Steps 4 and 5 (Stein and Myrdal, 2006).

In order to obtain a meaningful estimate of the residual particle size distribution, Steps 1–5 must be repeated for many droplets. Previous work has indicated that at least 5000 drug-containing droplets are required in order to obtain accurate size distribution measurements (Stein, 2008a). For the simulations reported in this paper, the model was created in Microsoft Visual Basic® 6.5 and embedded into Microsoft Excel® 2007 (Redmond, Washington, USA) with enough droplets in order to obtain at least 10,000 drug-containing droplets for each simulation. In the final step, titled "Output" in Fig. 2, an overall residual APSD is calculated based on residual aerodynamic diameter and mass outputs from each droplet included in the simulation. This algorithm was described briefly elsewhere (Stein et al., 2010), but each step in the algorithm is described in detail in Sections 2.2.1–2.2.7 along with any assumptions made.

A benefit of the algorithm is that it accounts for many of the differences in properties of the suspended drug particles. The residual aerosol for suspension pMDIs is influenced by the particle size distribution of the micronized drug powder, the density of the drug particles, and even the solubility of the drug in the formulation. All of these factors are taken into account in the algorithm. In reality, it is usually necessary to have very low drug solubility in the formulation in order to develop a stable suspension pMDI product. Therefore, it is reasonable in most cases to ignore (as the simulations reported in this paper do) the amount of drug dissolved in the formulation. Nevertheless, this algorithm provides the flexibility to model even complicated formulation scenarios.

2.1.1. Inputs: estimate of the initial droplet size distribution

One of the inputs required for the model is the initial size distribution of the atomized droplets. Previous research has shown that the initial droplet size distribution is dependent on the cosolvent concentration (typically ethanol) in a formulation, the actuator orifice diameter, and the valve size (Stein and Myrdal, 2004). For the simulations in this paper, Eq. (2) was used to estimate the MMD_I. The units associated with Eq. (2) are micrometers, so the droplet diameter was converted to centimeters in order to maintain consistency of units; centimeter–gram–second system of units was used in the program. The GSD_I was assumed to be 1.60 for all of the simulations based on previous research (Stein and Myrdal, 2004). Eq. (2) is an estimate of the initial droplet size distribution generated using solution pMDI formulations. In this paper it is being used to estimate the initial droplet size distribution for suspension pMDI formulations. Thus we are assuming that the presence of drug particles in the formulation does not sufficiently alter the atomization process to meaningfully change the size of the initial atomized droplets. It is difficult to experimentally verify this assumption due to the previously described challenges of experimentally measuring the initial droplet size distribution.

In order to predict the diameter of a given droplet from the initial droplet size distribution, the distribution must first be converted to a number-weighted size distribution. To do this, the initial droplet count median diameter (CMD_I) is calculated from the MMD_I obtained, using Eq. (2), by the Hatch–Choate equation (see Eq. (3); Hatch and Choate, 1929).

$$CMD_I = MMD_I \times e^{-3\times \ln^2 GSD_I} \quad (3)$$

2.1.2. Step 1 – determine size of the initial atomized droplet

The diameter of the initial droplet is calculated using a lognormal cumulative distribution function, assuming that the distribution of initial droplets follows a lognormal distribution. To do this, a random number, R, is sampled from a uniform distribution between 0 and 1. The size of the initial droplet, D_I, is then set to the droplet diameter that corresponds to the value of R from the inverse cumulative distribution function using the "LOGINV" function in Excel. When the value of R is 0.5, then the diameter of the droplet would be equal to the median diameter from the lognormal distribution curve (i.e. the diameter would be equal to CMD_I). An R-value that is very close to 0 (i.e. 0.001) results in a very small initial droplet diameter and an R-value that is very close to 1 (i.e. 0.999) results in an initial droplet diameter that is on the large diameter "tail" of the lognormal size distribution described by CMD_I and GSD_I. Once the diameter of the initial droplet is determined, the

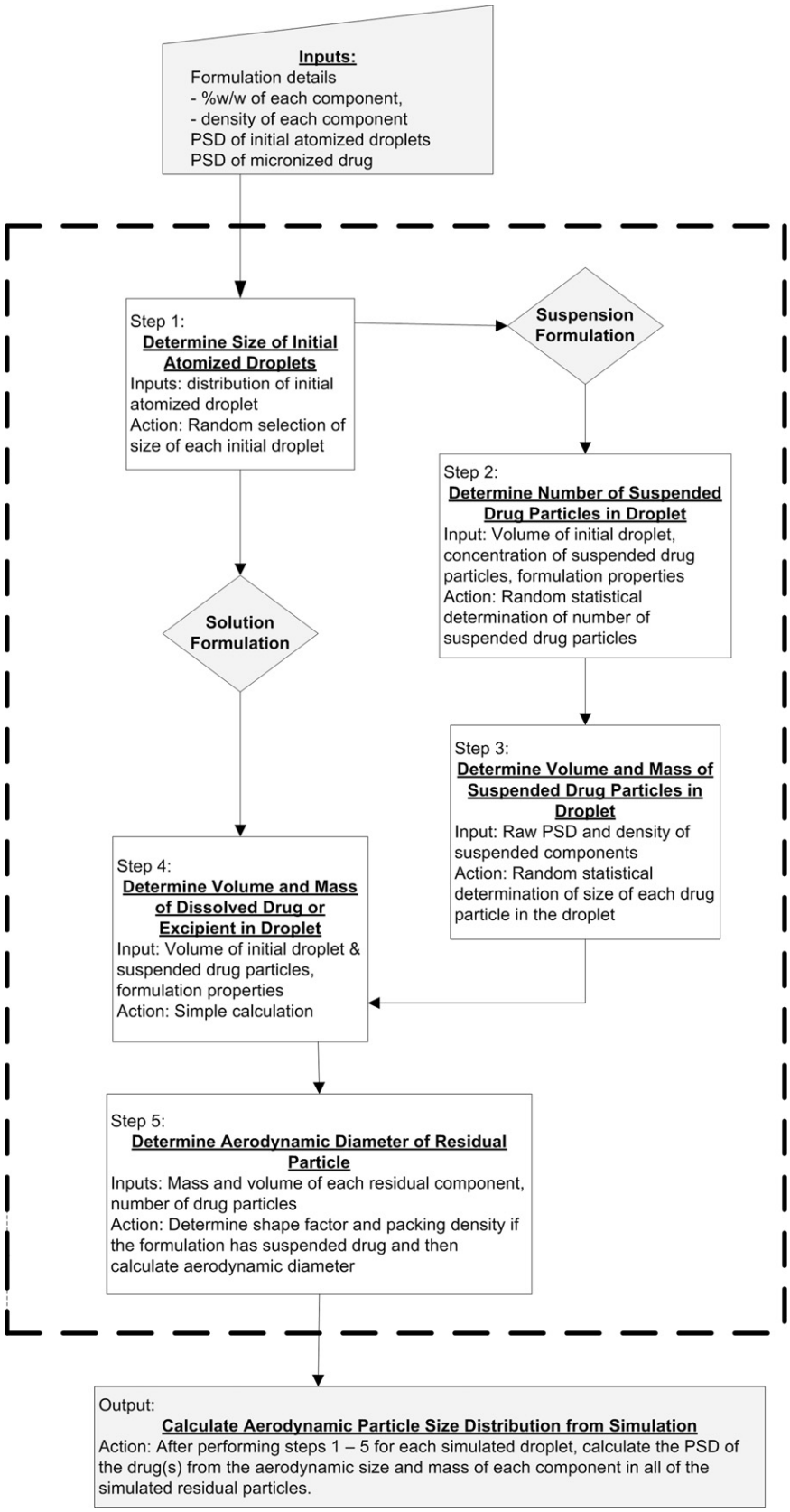

Fig. 2. Algorithm for simulating residual particle aerodynamic size distributions from suspension or solution pMDIs. In this research, the model for determining residual particle distribution from suspension pMDIs has been explored in detail.

volume of the initial droplet can then be calculated using the basic geometrical equation describing the volume of a sphere (Eq. (4)).

$$V_I = \frac{1}{6}\pi D_I^3 \tag{4}$$

where V_I is the volume, and D_I is the diameter of a sphere, which is the value resulting from the lognormal cumulative distribution function.

2.1.3. Step 2 – determine number of suspended particles in the droplet

The likelihood that a droplet will contain one or more drug particles depends on volume of the droplet and the number of drug particles per unit volume of the formulation and can be described using the Poisson distribution statistical function. Large droplets have a higher probability of having one or more drug particles than small droplets. Similarly, droplets from formulations that contain a higher number of drug particles per volume of formulation are more likely to contain drug particles than are droplets of the same size for a formulation with fewer drug particles. In order to randomly determine the number of particles in a given droplet using a Poisson distribution, the number of particles per unit volume (PPUV, #/cm^3) in the formulation must first be calculated. To determine this, Eq. (5) can be used.

$$\text{PPUV} = \frac{6 \times C_D \times e^{4.5 \times \ln^2 \text{GSD}_D} \times \rho_I}{\pi \times (0.0001 \times \text{MMD}_D)^3 \times \rho_D} \tag{5}$$

where C_D is the concentration of the drug (weight fraction), ρ_D is the drug particle density, and GSD_D and MMD_D are the geometric standard deviation and mass median diameter, respectively, of the micronized drug.

Once the number of particles per unit volume and the initial droplet diameter are known, the Poisson distribution can be used to determine the number of drug particles in the droplet. The Poisson distribution, as described by Eq. (6), is a discrete distribution that presents the probability ($P(I)$) of a particular droplet containing some number of drug particles, I, given the average occurrence of the event, M (Gonda, 1985; Raabe, 1968).

$$P(I) = \frac{e^{-M} \times M^I}{I!} \tag{6}$$

It is assumed that each droplet's contents are independent of other droplets. M is the product of volume of the initial droplet (V_I from Eq. (4)) and PPUV (Eq. (5)), giving the average number of drug particles in a droplet of a specific size. Once the M is known, Eq. (6) is used to determine the fraction of the atomized droplets that contain 0, 1, 2, 3, etc., suspended drug particles. The number of particles in the droplet is then determined using a random number generator to sample based on these probabilities. The value of M is calculated for each droplet in the simulation since the volume of each droplet differs. It is also assumed that the drug particles are uniformly distributed within the bulk formulation. In real suspension formulations, particles flocculate and even form irreversible aggregates. Loose flocculates contained in the formulation will likely break apart during the atomization process, but irreversible aggregates will cause some deviation from the assumption of uniform particle distribution in the formulation. The influence of suspension quality on suspension pMDI delivery is outside the scope of this investigation.

2.1.4. Step 3 – determine the size of the suspended drug particles in the droplet

The characterization of drug particles suspended in any given droplet can be calculated in a manner similar to that of initial droplets. The diameter of each drug particle is calculated by random sampling from the micronized drug particle size distribution that is provided as an input to the program. This sampling is done by using a uniformly distributed random number generator to select a number between 0 and 1 and then using the Excel "LOGINV" function to calculate the inverse of the cumulative lognormal distribution function of drug particle size that corresponds to this random number. As with the initial droplet diameter determination, the number-weighted drug particle size distribution (CMD_D) and GSD_D is used in this step. This process is conducted independently for each drug particle in a given droplet. Using the diameter values obtained for each drug particle, and assuming that drug particles are spherical, the volume of each drug particle in a droplet can be calculated and summed to provide the total volume that the drug particles occupy in a droplet. If the volume of drug particles exceeds the volume of the initial droplet (an extremely unusual occurrence), then the volume of initial droplet is used in place of the volume of drug particles for further calculations. If the droplet has any drug particles, the mass of the drug particles can then be calculated by taking the product of the volume of the drug particles and density of the drug as presented in Eq. (7).

$$M_D = \sum_{i=1}^{n} M_i = \sum_{i=1}^{n} V_i \times \rho_D \tag{7}$$

where M_D is the total mass of drug contained in the droplet, M_i is the mass of any given drug particle i, V_i is the volume of that drug particle, and ρ_D is the drug particle density, which is assumed to be the same for all of the drug particles.

2.1.5. Step 4 – determine volume or mass of dissolved drug or excipient in droplet

In this step, the volume and mass of dissolved drug or excipient are calculated based on the difference in volumes of the initial droplet (Step 1) and drug particles (Step 3) and the formulation density and excipient concentration. The volume of the liquid portion of the initial droplet is simply the difference of the total volume of the initial droplet and the volume of the drug particles in that droplet. The mass of the liquid can be determined by multiplying the volume of the liquid and density of the formulation, ρ_{form}, which is calculated as shown in Eq. (8).

$$\rho_{\text{form}} = \left(\sum_{i=1}^{n} \frac{C_i}{\rho_i} \right)^{-1} \tag{8}$$

where C_i is the weight fraction of some component, i, and ρ_i is the density of that component. The density of the formulation is the reciprocal of the sum of the ratio of the weight fraction to the density of the component for each ingredient in the formulation (Stein and Myrdal, 2004).

The mass of the dissolved drug and excipients is equal to the mass of the liquid portion of the initial droplet multiplied by the weight fraction of excipient in the formulation. The volume of the dissolved drug and excipients can then be determined by dividing the mass of the dissolved drug and excipients by its density.

2.1.6. Step 5 – determine aerodynamic diameter of residual particle

The last step for a given droplet is to calculate the aerodynamic diameter for each drug-laden residual particle based on its density (ρ_R, Eq. (9)) and volume equivalent diameter (d_v, Eq. (10)).

$$\rho_R = \frac{M_R}{V_R} = \frac{M_E + M_D}{V_E + V_D} \tag{9}$$

where M_R is the mass of the residual which is the sum of the mass of any dissolved excipient determined in Step 4 (M_E) and mass of drug particles determined in Step 3 (M_D) in the particle and V_R is

the volume of the residual which is the sum of the volume of the excipient (V_E) and volume of the drug (V_D).

$$d_v = \left(\frac{6 \times V_R}{\pi}\right)^{1/3} \quad (10)$$

Furthermore, for droplets containing two or more drug particles, a shape factor and packing density, are considered. The shape factor accounts for differences in the aerodynamic properties for spherical and non-spherical residual particles. Previous work to estimate shape factors has been done by Cheng et al. (1993) and Davies (1979). Cheng et al. measured the dynamic shape factor parallel to air flow experimentally by using various sized monodisperse PSL in aerosols from nebulized aqueous suspensions. However, due to the experimental limitation of the testing methods, they only obtained reasonable estimates of the shape factor for agglomerates of up to four particles. On the other hand, Davies developed a theoretical model for determining shape factor, which is utilized in this paper for droplets containing five or more drug particles. The packing density, a factor of 0.741, accounts for the difference in residual particle density based on void volume that is not occupied by the drug particles. If the droplet contains four drug particles or less, Eqs. (9)–(11) are used to calculate aerodynamic diameter of the residual particle (Cheng et al., 1993). The value for shape factor used with Eqs. (9)–(11) is taken to be 1.0, 1.0, 1.022, 1.08 and 1.12 for droplets containing 0, 1, 2, 3 and 4 drug particles, respectively (Cheng et al., 1993).

$$AD_R = d_v \times \left(\frac{\rho_R}{\text{shape} \cdot \text{factor}}\right)^{1/2} \quad (11)$$

where AD_R is the aerodynamic diameter of the residual particle, and the shape factor is determined as described above based on the number of drug particles contained within the residual particle.

If the droplet contains greater than four drug particles, Eqs. (12)–(14) are used to calculate aerodynamic diameter of the residual particle (Davies, 1979). For droplets containing 5, 6, 7, 8 and 9 drug particles the shape factors are considered to be 1.07, 1.05, 1.08, 1.10 and 1.10, respectively as given by Davies (1979). For droplets having 10–21 drug particles the shape factor stays relatively constant from 1.12 to 1.14 (Davies, 1979) and droplets having more than 21 drug particles the shape factor remains constant at 1.10.

$$d_{cluster} = \left(\frac{6 \times V_D}{0.741 \times \pi}\right)^{1/3} \quad (12)$$

where $d_{cluster}$ is the volume equivalent diameter of the cluster.

$$\rho_{cluster} = \frac{M_D + M_E}{V_D} \times 0.741 \quad (13)$$

where $\rho_{cluster}$ is the density of the cluster.

$$AD_R = d_{cluster} \times \left(\frac{\rho_{cluster}}{\text{shape} \cdot \text{factor}}\right)^{1/2} \quad (14)$$

2.1.7. Output – calculate aerodynamic particle size distribution from simulation

Steps 1–5 are repeated until at least 10,000 residual particles containing drug are obtained. Since many of the atomized droplets do not contain any drug, more than 10,000 droplets are modeled. Once the sufficient drug-containing residual particles are obtained, the simulation is stopped and the drug residual particle size distribution is calculated. This is done by sorting the droplets by aerodynamic particle size and summing the mass of drug particles for all of the droplets contained in each given size bin. The residual particles are sorted into 20 different size bins based on their aerodynamic diameter. Twenty bins were selected in order to provide adequate resolution of the residual particle size distribution. More or less bins could be selected if desired. The total mass of each formulation component contained in all of the residual particles is calculated for each size bin. In this way, the mass of drug in each of the size bins can be determined. This is used to calculate the aerodynamic particle size distribution of the drug delivered in the residual aerosols. In a similar fashion, it would be possible to determine the aerodynamic particle size distribution of the dissolved excipient delivered in the residual aerosols, but this is usually not desired. A commercial fitting program (DISTFIT™, Chimera Technologies, Forest Lake, MN) is used to calculate the MMAD and GSD of the aerosol. For most formulations, the data is fitted using a unimodal lognormal distribution, as the residual particle distribution usually has only one mode. However, for complex formulations (i.e. combination formulations with two different drugs included in the formulation or formulations with both suspended and dissolved drug) this simplifying assumption may not be valid. A chi-square goodness-of-fit test was used to assess the lognormal distribution; an α-level of <0.02 was considered indicate a good level of fit for the unimodal lognormal distribution.

2.2. Experimental materials and method

Albuterol sulfate micronized to varying particle sizes was provided by 3M Drug Delivery Systems (St. Paul, MN, USA) and Micron Technologies Ltd. (Dartford, Kent, UK). Valves and actuators were provided by 3M Drug Delivery Systems and pressure resistant glass vials were purchased from Research Products International Corporation (Mt. Prospect, IL, USA). HPLC-grade methanol and phosphoric acid were purchased from Sigma–Aldrich (St. Louis, MO, USA). 200 proof ethanol was purchased from Decon Labs (King of Prussia, PA, USA) and HFA-134a, from Atofina Chemicals Incorporated (Philadelphia, PA, USA).

2.2.1. Determining APSD of micronized drug

The particle size distribution of two of the lots of micronized albuterol sulfate used in the experimental formulations was measured using the Model 3321 Aerodynamic Particle Sizer Spectrometer™ (APS) in conjunction with the Model 3433 Small Scale Powder Disperser (both from TSI Inc., Shoreview, MN, USA). The first drug lot had an MMAD of 2.62 μm and a GSD of 1.81. The second lot had an MMAD of 1.77 μm and a GSD of 1.57.

The third drug lot was obtained by high shear homogenization of the first drug lot in 200 proof ethanol using a technique described elsewhere (Jinks, 2003; James et al., 2008). After high shear homogenization, the particle size of the albuterol sulfate in the resultant ethanol slurry was measured using the Malvern Mastersizer 2000 particle size analyzer (Malvern Instruments Ltd., Malvern, Worcestershire, UK). Prior to the size measurement, the slurry was diluted by adding additional 200 proof ethanol in order to get the particle concentration in the appropriate range for the instrument. The size of the micronized drug in the slurry was measured to have an MMD of 1.06 μm and a GSD of 1.57. Since micronized albuterol sulfate has a density of approximately 1.25 g/cm^3, the MMAD for this drug lot is approximately 1.22 μm.

2.2.2. Formulation of pMDIs

Twelve suspension pMDIs, containing 0.01–1% (w/w) of varying sizes of micronized albuterol sulfate and approximately 8.5% (w/w) 200 proof ethanol in HFA-134a were prepared in pressure resistant glass vials (see Table 1). Once the glass vials contained the desired amount of ethanol and micronized drug, a cold-transfer technique was used to fill the vials with HFA-134a. Each of the vials was immediately crimped with a 50 μL valve using a small-scale bottle crimper. Vials were sonicated for 60 s to disperse the suspension.

Table 1
Pressurized MDI formulations used for experimental size distribution measurements with the ACI along with the number of actuations used during ACI testing.

Micronized drug size (MMAD (μm); GSD)	Drug concentration (% w/w)	Ethanol concentration (% w/w)	Actuations (#)
1.22 μm; 1.57	0.0093	8.9	25
	0.0883	8.7	15
	0.215	8.7	10
	0.878	8.6	3
1.77 μm; 1.57	0.0328	8.2	25
	0.107	8.2	15
	0.412	8.2	5
	1.028	9.0	2
2.62 μm; 1.81	0.0333	8.6	25
	0.116	8.4	15
	0.409	8.2	5
	1.096	8.7	2

2.2.3. Andersen cascade impactor (ACI) testing

Prior to each run, the stages of the ACI were thoroughly rinsed with 50% (v/v) methanol:water followed by 100% methanol and dried in a stream of dry air. Once dry, the stages and the throat were coated with 50:50 methanol:pluronic L10. QVAR® actuators, with an orifice diameter of 0.3 mm, were used for all of the testing. For each experiment in the series, the sample vial was actuated three times in order to prime the valve; the stem of the valve was subsequently cleaned with the diluent (77:23 water:methanol). The valve stem and actuator were then dried and the vial was fitted to the clean actuator. The flow rate through the ACI was adjusted to 28.3 L/min using a TSI Series 4000 flow meter (TSI Inc., Shoreview, MN, USA). Triplicate ACI analyses were done using each vial. In order to have sufficient drug on the stages of the ACI for accurate quantification of the drug, the number of actuations for each vial varied between 2 and 25 based on the concentration of the formulation (see Table 1). The valve stem, actuator, USP throat, stages 0–7, and the filter were rinsed with appropriate volumes of the diluent and the amount of drug present on each stage was determined by high performance liquid chromatography (HPLC).

2.2.4. Analytic assay

The HPLC system consisted of a Waters 2690 Separations module coupled with a Waters 996 PDA. An Apollo C18 5 μm 150 mm × 4.6 mm column, maintained at 30 ± 2 °C, was used. 1% phosphoric acid:methanol (77:23 v/v) was used as the mobile phase at a flow rate of 0.75 mL/min with an injection volume of 40 μL. The data was collected and processed utilizing Millennium Version 3.20 with UV detection at 225 nm. Quantitation was conducted based on peak area using a standard curve with a linear region between 0.250 and 250 μg/mL albuterol sulfate. The total run time was 5 min per sample and the retention time for albuterol sulfate was 3.3 min. No leachable and extractable compounds were detected from the vials or bags used to rinse the ACI stages upon analysis of the HPLC data.

2.2.5. Determining APSD of residual particles

The HPLC results from the ACI test were used to determine the APSD of the drug delivered in the residual aerosols. DISTFIT was used to determine the MMAD and GSD of the aerosol and the aerosol was assumed to be a unimodal lognormal distribution. For the formulations described in Table 1, the residual particle size distributions all fit the unimodal lognormal distribution reasonably well. No size information is available for the portion of the drug that deposited on the valve stem, actuator, and USP inlet and these were thus not included in the APSD calculations.

3. Results and discussion

3.1. Sample output from suspension pMDI model

Simulations were made using the model shown in Fig. 2 for a variety of pMDI formulation configurations. Sample output from two different configurations are shown in Tables 2 and 3. Both of these tables show the first 25 droplets from separate simulations. The first two columns show the diameter and volume, respectively, of the initial droplet for each configuration. The volume and mass of the drug particles and surfactant in each droplet are shown in the fourth through seventh columns. Aerodynamic diameter is shown in the last column. Once the desired number of droplets have been simulated and the droplets are sorted according to their residual particle aerodynamic diameter, the information in column five (mass of drug particles) and the last column (aerodynamic diameter) are used to calculate the aerodynamic particle size distributions of the drug. Note that many of the droplets contain zero drug mass since they do not contain any suspended drug particles in the droplet.

For the pMDI configuration in Table 2, two of the three droplets that did contain drug particles had just a single drug particle, but the other droplet had 11 drug particles. For the configuration in Table 2, the MMD_I calculated and used in the simulation was 10.7 μm based on Eq. (2) and the details of the formulation, valve size, and actuator orifice. Most of the droplets are smaller than this (the CMD_I for this configuration was 3.8 μm). As expected based on the properties of the Poisson statistical distribution function, larger droplets were more likely to contain one or more drug particles. The largest droplet was the droplet that contained 11 drug particles. This droplet was approximately eight times larger by volume than any of the other droplets in Table 2. However, not all large droplets contain drug and some relatively small droplets do contain drug. For example, a droplet with an initial diameter of 3.6 μm had a drug particle whereas a different droplet with an initial diameter of 8.2 μm had no suspended drug particles. This seemingly unusual result is simply a result of the random sampling based on the Poisson distribution probabilities.

The difference in the size of the drug particles from the simulations can be seen in Table 2 by the fact that the mass of drug particles in the two droplets containing a single drug particle varied by more than a factor of 15. For the droplets containing no drug particles, the final aerodynamic diameter is essentially proportional to the diameter of the initial droplet. For the droplets containing drug, the final aerodynamic diameter is primarily controlled by the mass of the drug particles. The droplet with the 11 drug particles had the largest residual particle aerodynamic diameter (2.53 μm).

Table 2
Output from the first 25 droplets simulated for a formulation with 0.4% (w/w) suspended drug with an MMAD of 2.5 μm and GSD of 1.6, 8.5% (w/w) ethanol, 0.02% (w/w) oleic acid, 91.1% HFA-134a, 50 μL valve, and actuator orifice diameter of 0.3 mm.

Diameter of droplet (μm)	Droplet volume (cm^3)	# of drug particles in droplet	Volume of drug particles (cm^3)	Mass of drug particles (g)	Mass of surfactant (g)	Volume of surfactant (cm^3)	Mass of residual particle (g)	Residual particle aerodynamic diameter (μm)
5.948	1.102E−10	0	0	0	2.535E−14	2.028E−14	2.535E−14	0.378
3.291	1.866E−11	0	0	0	4.292E−15	3.434E−15	4.292E−15	0.209
1.214	9.364E−13	0	0	0	2.154E−16	1.723E−16	2.154E−16	0.077
1.158	8.134E−13	0	0	0	1.871E−16	1.497E−16	1.871E−16	0.074
5.482	8.628E−11	0	0	0	1.985E−14	1.588E−14	1.985E−14	0.349
2.989	1.399E−11	0	0	0	3.217E−15	2.574E−15	3.217E−15	0.190
2.750	1.089E−11	0	0	0	2.505E−15	2.004E−15	2.505E−15	0.175
3.574	2.390E−11	1	2.031E−12	3.046E−12	5.031E−15	4.025E−15	3.051E−12	1.925
8.211	2.899E−10	0	0	0	6.668E−14	5.334E−14	6.668E−14	0.522
2.159	5.273E−12	0	0	0	1.213E−15	9.703E−16	1.213E−15	0.137
3.247	1.793E−11	0	0	0	4.124E−15	3.300E−15	4.124E−15	0.207
2.590	9.096E−12	0	0	0	2.092E−15	1.674E−15	2.092E−15	0.165
4.301	4.166E−11	0	0	0	9.582E−15	7.666E−15	9.582E−15	0.274
10.447	5.969E−10	1	1.327E−13	1.991E−13	1.373E−13	1.098E−13	3.363E−13	0.911
5.296	7.778E−11	0	0	0	1.789E−14	1.431E−14	1.789E−14	0.337
3.905	3.118E−11	0	0	0	7.172E−15	5.738E−15	7.172E−15	0.248
2.308	6.434E−12	0	0	0	1.480E−15	1.184E−15	1.480E−15	0.147
3.522	2.288E−11	0	0	0	5.263E−15	4.211E−15	5.263E−15	0.224
21.095	4.915E−09	11	5.188E−12	7.782E−12	1.130E−12	9.036E−13	8.911E−12	2.532
2.015	4.286E−12	0	0	0	9.859E−16	7.887E−16	9.859E−16	0.128
6.094	1.185E−10	0	0	0	2.726E−14	2.180E−14	2.726E−14	0.388
10.469	6.007E−10	0	0	0	1.382E−13	1.105E−13	1.382E−13	0.666
1.747	2.790E−12	0	0	0	6.418E−16	5.134E−16	6.418E−16	0.111
0.861	3.338E−13	0	0	0	7.678E−17	6.142E−17	7.678E−17	0.055
3.762	2.787E−11	0	0	0	6.412E−15	5.129E−15	6.412E−15	0.239

Comparing the results in Tables 2 and 3 illustrates the impact that the concentration of suspended drug particles has on the percentage of droplets that contain drug particles and the percentage of multiplets. The concentration of suspended drug particles per unit volume increases proportionally with increasing drug concentration in the formulation and increases according to the third power with decreasing input drug size. Thus, the formulation in Table 3 has approximately 4.6 times (i.e. 1.67 to the third power) as many suspended drug particles in the formulation as that represented in Table 2, since the input drug size for the formulation in Table 2 is 1.67 times larger than that for the formulation in Table 3. Not surprisingly, the formulation in Table 3 has more droplets

Table 3
Output from the first 25 droplets simulated for a formulation with 0.4% (w/w) suspended drug with an MMAD of 1.5 μm and GSD of 1.6, 8.5% (w/w) ethanol, 0.02% (w/w) oleic acid, 91.1% HFA-134a, 50 μL valve, and actuator orifice diameter of 0.3 mm.

Diameter of droplet (μm)	Droplet volume (cm^3)	# of drug particles in droplet	Volume of drug particles (cm^3)	Mass of drug particles (g)	Mass of surfactant (g)	Volume of surfactant (cm^3)	Mass of residual particle (g)	Aerodynamic diameter (μm)
4.400	4.461E−11	2	3.461E−14	5.192E−14	1.030E−14	1.151E−14	6.222E−14	0.511
3.387	2.034E−11	0	0	0	4.703E−15	5.254E−15	4.703E−15	0.204
1.926	3.741E−12	0	0	0	8.648E−16	9.662E−16	8.648E−16	0.116
3.805	2.884E−11	0	0	0	6.666E−15	7.448E−15	6.666E−15	0.229
1.261	1.050E−12	0	0	0	2.428E−16	2.713E−16	2.428E−16	0.076
5.597	9.180E−11	2	3.892E−14	5.838E−14	2.121E−14	2.370E−14	7.959E−14	0.549
3.110	1.574E−11	1	1.046E−13	1.569E−13	3.615E−15	4.040E−15	1.605E−13	0.720
2.618	9.399E−12	0	0	0	2.173E−15	2.427E−15	2.173E−15	0.158
3.355	1.978E−11	0	0	0	4.573E−15	5.109E−15	4.573E−15	0.202
1.105	7.059E−13	0	0	0	1.632E−16	1.823E−16	1.632E−16	0.067
6.638	1.531E−10	2	3.533E−14	5.300E−14	3.539E−14	3.954E−14	8.838E−14	0.562
4.848	5.966E−11	0	0	0	1.379E−14	1.541E−14	1.379E−14	0.292
2.747	1.085E−11	0	0	0	2.508E−15	2.803E−15	2.508E−15	0.165
2.850	1.212E−11	0	0	0	2.802E−15	3.131E−15	2.802E−15	0.172
3.162	1.655E−11	0	0	0	3.825E−15	4.274E−15	3.825E−15	0.190
2.215	5.689E−12	0	0	0	1.315E−15	1.469E−15	1.315E−15	0.133
10.336	5.782E−10	7	4.017E−13	6.026E−13	1.336E−13	1.492E−13	7.361E−13	1.135
1.330	1.233E−12	0	0	0	2.850E−16	3.184E−16	2.850E−16	0.080
2.920	1.303E−11	0	0	0	3.013E−15	3.366E−15	3.013E−15	0.176
1.039	5.867E−13	0	0	0	1.356E−16	1.515E−16	1.356E−16	0.063
1.640	2.308E−12	0	0	0	5.336E−16	5.962E−16	5.336E−16	0.099
12.495	1.021E−09	22	1.487E−12	2.231E−12	2.358E−13	2.634E−13	2.467E−12	1.656
5.456	8.502E−11	1	5.425E−14	8.138E−14	1.964E−14	2.194E−14	1.010E−13	0.606
1.869	3.421E−12	0	0	0	7.907E−16	8.835E−16	7.907E−16	0.113
2.372	6.992E−12	0	0	0	1.616E−15	1.806E−15	1.616E−15	0.143

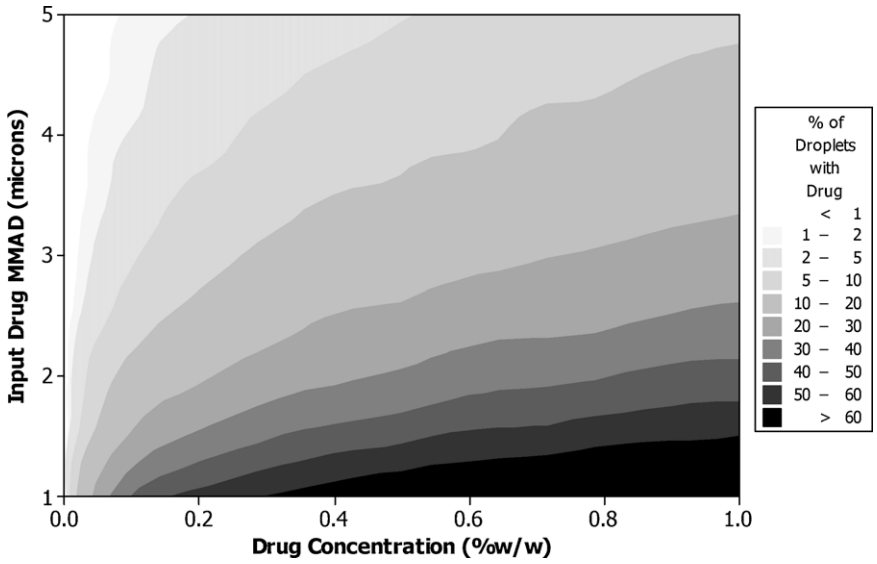

Fig. 3. The percentage of atomized droplets containing one or more drug particles from simulations using different drug concentrations and input drug sizes.

which contain drug (seven compared to three) and more multiplets (five versus one) than the formulation in Table 2.

3.2. Factors influencing whether droplets contain drug particles

3.2.1. Does the droplet contain any drug?

Simulations were made on many formulations in order to gain insight into the number of atomized droplets that contain one or more drug particles. In order to do this, the drug concentration was varied from 0 to 1% (w/w) and the input drug MMAD was varied from 1 to 5 μm. For all of the formulations, the input drug GSD was set to 1.6, the ethanol concentration to 8.5% (w/w), no surfactant was included, HFA-134a was the propellant, the valve size was set to 50 μL, and the actuator orifice diameter to 0.3 mm. Fig. 3 shows the percentage of the atomized droplets that contain one or more drug particles for these simulations. Both the drug concentration and the input drug size significantly influence the percentage of atomized droplets containing drug, but the influence is most significant for the input drug size. Most commercial suspension MDI formulations have input drug with MMADs between about 2 and 5 μm and concentrations less than about 0.5% (w/w) drug. For these formulations, less than about 30% of the atomized droplets contain drug. In many cases, less than 10% of the atomized droplets contain drug particles.

3.2.2. How many drug particles does a droplet contain?

Drug concentration and input drug size not only influence how many of the droplets contain drug particles, but they also significantly influence how many of the droplets are multiplets. Fig. 4 illustrates this for four of the formulations used to create Fig. 3. The

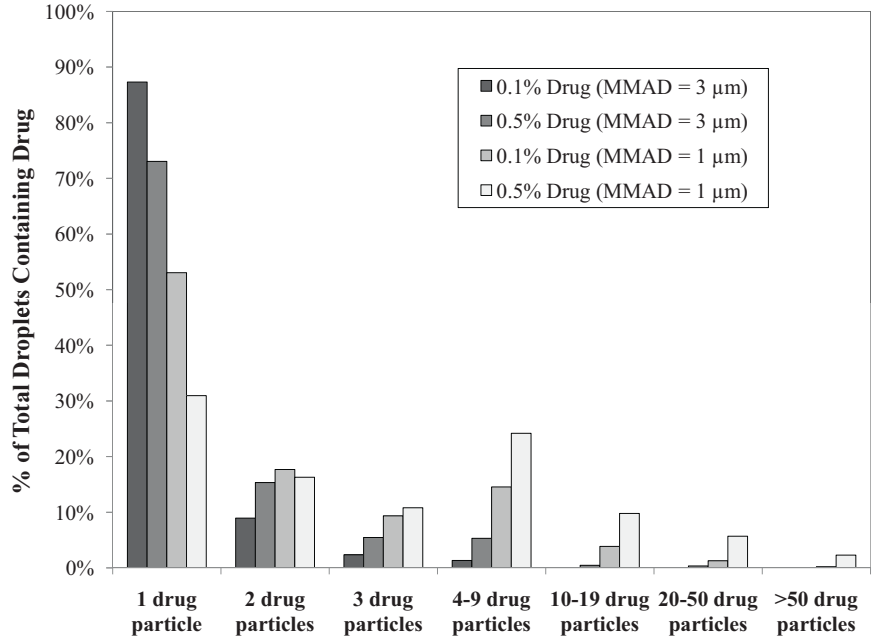

Fig. 4. The percentage of the total droplets containing drug plotted as a function of the number of drug particles in the droplet shown for pMDI configurations with varying micronized drug size and concentration in % (w/w). For all four configurations simulated, the valve size used was 50 μL, the orifice diameter was 0.3 mm, the ethanol concentration was 8.5% (w/w), and the propellant was HFA-134a.

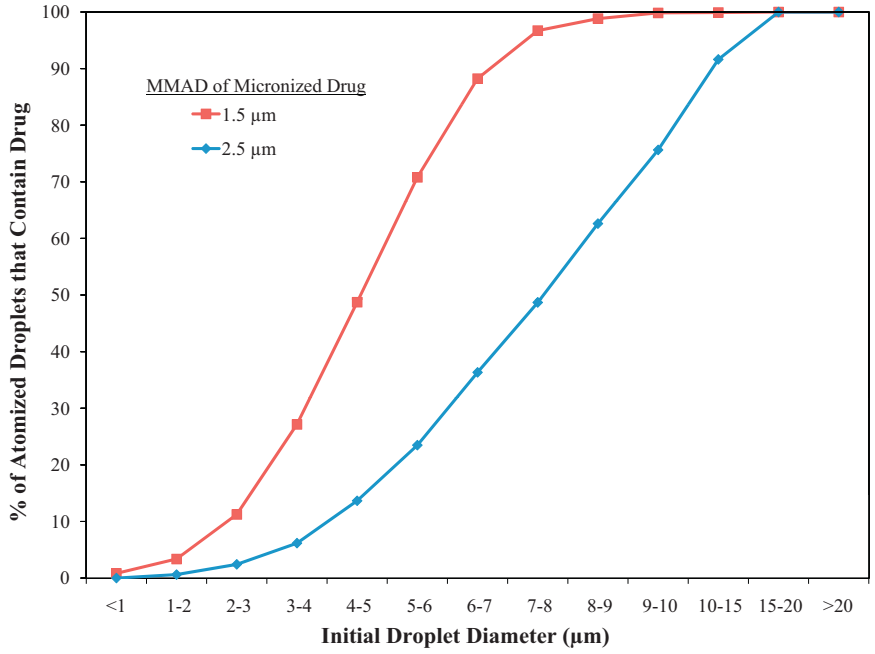

Fig. 5. The percentage of atomized droplets containing at least one drug particle for the simulations shown in Tables 2 and 3. Both formulations contain 0.4% (w/w) drug.

majority of the droplets that do contain drug have a single drug particle. This is particularly true for simulated formulations that used an input drug MMAD of 3 μm. For the formulation with an input drug size of 3 μm and 0.1% (w/w) drug, 87% of the drug-containing droplets had just a single drug particle, 9% contained two drug particles, and just 4% of the drug-containing droplets had more than two drug particles. The formulation with an input drug MMAD of 1.0 μm and 0.5% (w/w) drug had a far greater proportion of multiplets. For this formulation, only 31% of the droplets containing drug had a single drug particle compared to 69% which were multiplets. This formulation had many large multiples. Approximately 5.7% of the drug-containing droplets had between 20 and 50 drug particles and about 2.3% of the droplets had more than 50 drug particles. While only about 8.0% of the drug-containing droplets had more than 20 drug particles, these droplets contained 54% of the total drug particle mass and thus can significantly impact the overall residual aerosol size distribution. The residual particle sizes of the droplets containing many drug particles are smaller than one might anticipate. For example, one of the droplets in the simulation of the formulation with 0.5% of the 1.0 μm MMAD input drug contained 606 drug particles in the droplet. Despite having 606 drug particles, the residual particle aerodynamic diameter was

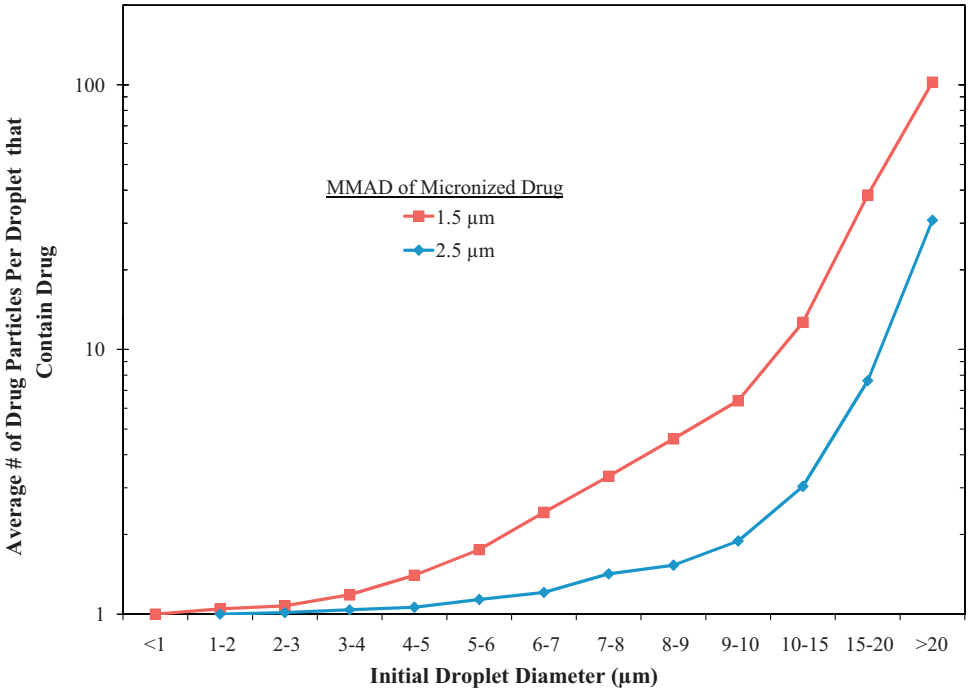

Fig. 6. The average number of drug particles per droplet containing drug for the simulations shown in Tables 2 and 3. Both formulations contained 0.4% (w/w) drug.

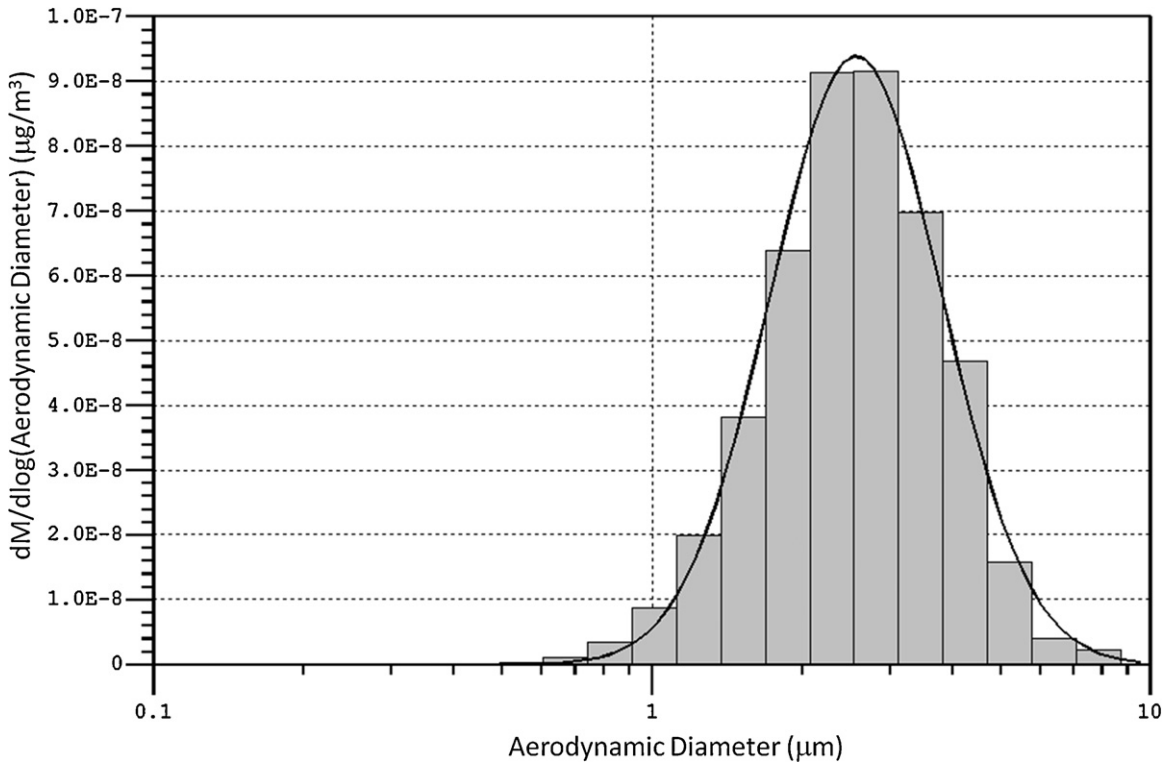

Fig. 7. The residual particle size distribution of drug obtained from a simulation with 0.4% (w/w) suspended drug with an MMAD of 2.5 μm and GSD of 1.6, 8.5% (w/w) ethanol, 0.02% (w/w) oleic acid, 91.1% HFA-134a, 50 μL valve, and 0.3 mm actuator orifice diameter.

only 5.5 μm. It should be noted that particle diameter is not additive for clusters of many drug particles, but rather drug volume and mass are additive and particle diameter increases with drug mass to the one-third power. Additionally, most of the individual drug particles from an input size distribution with a mass median aerodynamic diameter of 1.0 μm are substantially smaller than 1.0 μm. As a result, some of these large multiplet particles end up being of an aerodynamic particle size capable of reaching the lung.

3.2.3. *The influence of initial droplet size*

The data from the full simulations represented in Tables 2 and 3 was analyzed to understand the influence of initial droplet size on the likelihood that droplets have at least one drug particle (Fig. 5) or have multiple drug particles (Fig. 6). Larger droplets were much more likely to have suspended drug particles than smaller droplets (Fig. 5). More of the droplets contained drug for the formulation with the smaller input drug size compared to the formulation with

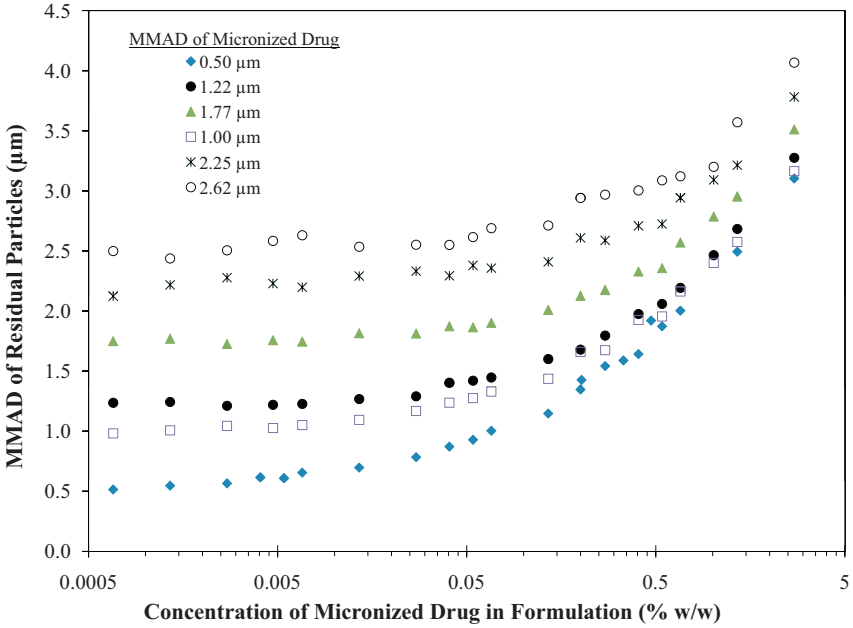

Fig. 8. The MMAD obtained from simulations of formulations with varying drug concentrations and input drug size. All experiments assumed 50 μL valves, actuators with an orifice diameter of 0.3 mm, 8.5% (w/w) ethanol, no surfactant, and HFA-134a.

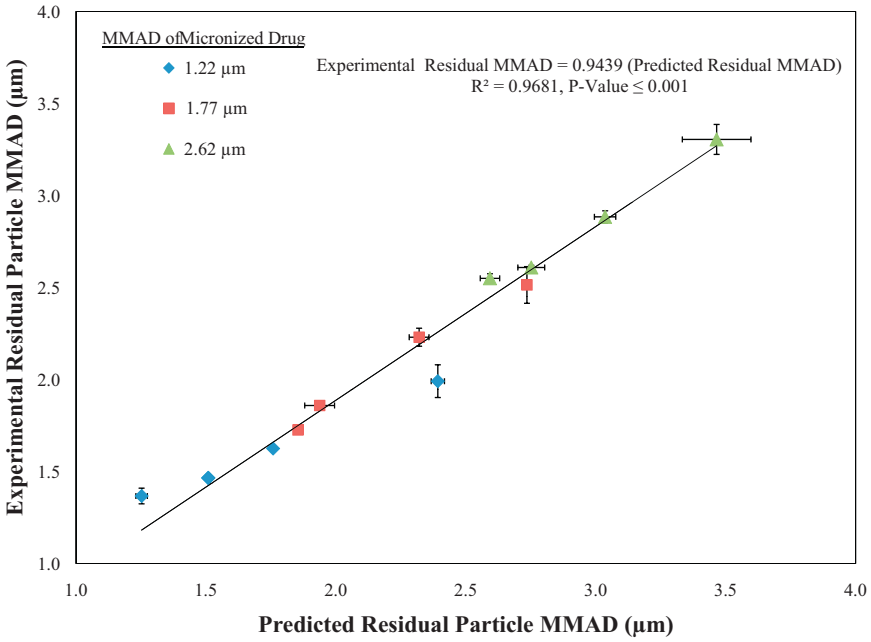

Fig. 9. A comparison of the predicted residual particle MMAD to the MMAD obtained from experimental measurements using the ACI for 12 suspension pMDI configurations.

the larger input drug size due to the fact that more total drug particles were present in the formulation (Eq. (5)). Larger atomized droplets and formulations with smaller input drug size had the highest probability of having multiple drug particles (Fig. 6). For the small fraction of droplets with initial diameters greater than 20 μm, large agglomerates having many drug particles were obtained. These clusters contained on average 102 and 31 drug particles for the formulations with 1.5 μm and 2.5 μm input drug MMAD, respectively.

3.3. Predicting residual particle size distributions for a variety of suspension MDI formulations

3.3.1. Example residual particle size distribution from a simulation

The aerodynamic size distribution from the complete simulation that is partially shown in Table 2 was calculated using DISTFIT software and is shown in Fig. 7 as a representative example of the size distribution results obtained using the model. The MMAD of the residual particles was estimated to be 2.92 μm and the GSD was estimated to be 1.63. This simulation contained 10,000 drug-containing droplets. The quality of the distribution is highly dependent on the number of drug-containing droplets in the simulation and tends to be of poorer quality (i.e. they are more variable and deviate more from a lognormal distribution) when less than 10,000 drug-containing droplets are included. The distribution shown in Fig. 7 was representative of a typical distribution obtained from most of the simulations reported in this paper.

3.3.2. The influence of input drug size and concentration on residual particle size distribution

Simulations were made for formulations with a wide range of input drug sizes and drug concentrations in the formulations. All of these simulations had 8.5% (w/w) ethanol, no surfactant, HFA-134a, and used 50 μL valves and actuators with an orifice diameter of 0.3 mm. The input drug sizes selected ranged from 0.5 to 2.62 μm MMAD. Three of the input particle sizes (1.22, 1.77, 2.62 μm MMAD) used in these simulations were selected due to the fact that albuterol sulfate with these particle sizes was available for experimental testing to compare the simulations to actual experiments (see Section 3.4). The residual particle MMADs from these simulations are shown in Fig. 8. The residual particle MMAD increases with increasing input drug size and drug concentration.

For the simulations using low drug concentrations the residual particle MMAD is essentially the same as the MMAD of the input drug. This indicates that the number of multiplets is sufficiently low as to have a minimal impact on the residual particle size distribution. As the drug concentration in the formulation increases, the residual particle MMAD increases due to the increased number of multiplets. The drug concentration at which the residual particle MMAD begins to noticeably deviate from the input drug size is lower for the smaller input drug size. This is due to the fact that at a given drug concentration there are more particles per unit volume for the smaller input drug size. Thus, there are more multiplets at a given drug concentration when a smaller input drug size is used (see Fig. 4, for example).

The difference that the input drug size has on the residual particle MMAD is less significant at higher drug concentrations. The relationship between input particle MMAD and residual particle MMAD is simple at low drug concentrations. However, the relationship is much more complex at higher drug concentrations. This can be seen by comparing the residual MMAD for formulations 1.0 and 2.25 μm input drug. For formulations with drug concentrations of 0.0013% (w/w), the residual particle MMAD was 2.22 times higher (2.22 μm compared to 1.00 μm) for formulation with 2.25 μm input drug. Thus, a 2.25-fold increase in input drug MMAD resulted in a 2.22-fold increase in residual particle MMAD. At the drug concentration of 1.0% (w/w), the 2.25-fold increase in input drug MMAD resulted only in a 1.29-fold increase in residual particle MMAD (3.09 μm compared to 2.40 μm)

There is some scatter in the simulations is due to the fact that these are random simulations with typically 10,000 drug-containing droplets (up to 30,000 in some cases). Most MDI products on the market, on the other hand, deliver tens to hundreds of millions of drug-containing droplets (Stein, 2008b). Simulation with larger sample sizes can be used to reduce the variability in the estimated residual particle MMAD (Stein, 2008a), but increase computational requirements and thus reduce the number of simulations that can be run in a given amount of time.

3.4. Comparison of simulated and experimental particle size distributions

Experimental measurements were made from pMDIs using the formulations described in Table 1 with QVAR actuators and 50 μL Spraymiser™ valves. The residual APSDs were measured using the ACI. The residual APSDs were also simulated for these same pMDI configurations. The pMDI configurations examined consisted of a range of different input drug sizes (MMADs from 1.22 to 2.62 μm) and a broad range of drug concentrations (less than 0.01 to greater than 1%, w/w). Fig. 9 shows a comparison of the experimental and simulated APSDs. There was good agreement between the MMAD values predicted in the simulations and those measured from the ACI ($r^2 = 0.97$) demonstrating the utility of the algorithm for predicting residual APSDs for a broad range of suspension pMDI configurations.

4. Conclusions

A model for predicting the aerodynamic particle size distributions delivered from a variety of pMDIs formulations was developed. This model expands on the models developed by Gonda (1985) and Chan and Gonda (1988) by allowing for polydisperse micronized input drug to be included in the simulation, dissolved drug and/or excipient to be included in the formulation, and the initial droplet size distribution used in the simulation to be estimated based on empirical equations for HFA-134a formulations (Stein and Myrdal, 2004). The model calculates the aerodynamic diameter of residual particles obtained from atomized droplets after evaporation of the volatile components of the pMDI formulation. Key inputs needed for this simulation are complete details of the formulation composition, the size distribution of any micronized drug(s) included in the formulation, and optionally the initial size distribution of the atomized droplets.

The model was used to evaluate drug delivery from suspension pMDIs. The model indicated that the majority of atomized droplets do not contain micronized drug particles in them. For these droplets, the residual particles contain only surfactant or any other non-volatile excipient or drug dissolved in the formulation. Typically, less than 30% of the atomized droplets contain micronized drug; however, for many formulations, less than 10% of the atomized droplets contain drug. The percentage of droplets containing drug is sensitive to the drug concentration and very sensitive to the input drug size.

For typical suspension pMDI configurations (with micronized drug having an MMAD > 2 μm and a drug concentration less than about 0.5%, w/w), the vast majority of the atomized droplets that do contain micronized drug particles contain just a single drug particle. For example, less than 13% of the residual particles with drug were multiplets for a suspension pMDI containing 0.1% (w/w) of micronized drug with an MMAD of 3 μm. The proportion of the multiplets increases for formulations with higher drug concentrations and smaller input drug sizes. For example, 69% of the residual particles with drug were multiplets for a suspension pMDI containing 0.5% (w/w) of micronized drug with an MMAD of 1 μm. For suspension pMDIs that result in residual particles with few multiplets, the size distribution of the residual aerosol delivered to the patient is essentially equal to the size distribution of the micronized drug. On the other hand, suspension pMDIs containing smaller micronized drug and/or higher drug concentrations have a higher proportion of multiplets which in turn can result in a substantially larger MMAD of the residual aerosol compared to the MMAD of the micronized drug.

In order to demonstrate the utility of the model, size distributions predicted using the model for 12 different suspension pMDI configurations were compared to experimental cascade impactor measurements of the aerosol delivered from equivalent suspension pMDIs. The size of the micronized drug was varied from 1.22 to 2.62 μm and a wide range of drug concentrations (less than 0.01 to greater than 1%, w/w) were used. On average, the model slightly overestimated the residual particle MMAD by about 6%. However, over this broad range of suspension pMDI configurations, the size distributions predicted by the model closely agreed with the experimental measurement ($r^2 = 0.97$). The close agreement between the predicted and experimentally measured residual particle size distributions demonstrates the utility of this model for predicting suspension pMDI size distributions. In the future, additional work should be done to demonstrate the utility of this model for predicting the particle size distributions for more complex pMDI formulations such as formulations containing multiple suspended drugs or formulations with one suspended drug and one dissolved drug.

Acknowledgements

The authors thank Chris Karayiannis of Micron Technologies Ltd. for providing micronized albuterol sulfate with MMAD of 2.62 μm with a GSD of 1.81 for ACI testing, Herbert Chiou of 3M Drug Delivery Systems for assisting with sizing of the micronized drug, and Nimish Sheth of the University of Arizona with help generating ACI data.

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