ELSEVIER

International Journal of Pharmaceutics 113 (1995) 123–130

international journal of pharmaceutics

Testing of dry powder aerosol formulations in different environmental conditions

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Received 4 March 1994; modified version received 22 June 1994; accepted 24 June 1994

Abstract

Dry powder aerosol performance of albuterol and albuterol sulfate from a model dry powder inhaler (DPI) was studied under varying environmental conditions using a twin stage impinger (TSI). Pure micronized drug was metered into the DPI and the loaded inhaler inserted into the inlet of the TSI housed in a pre-equilibrated environmental chamber. After 3 min, the drug was aerosolized at 60 l/min for 20 s. Washings from the DPI and TSI were analyzed by UV spectroscopy. Temperature and relative humidity (RH) were varied (20, 30 and 45°C; 30–95% RH). Drug collected in stage 2 of the TSI was expressed as fine particle dose or fine particle percent of either the loaded dose or the amount emitted from the mouthpiece of the DPI. These values decreased with increasing relative humidity for both albuterol and albuterol sulfate at any given temperature with differences being more marked at higher temperatures. For example, at 30°C, the mean(experimental range) fine particle percent of the emitted dose of albuterol sulfate was 59.4(3.1) and 35.8(5.7)% at 43 and 85% RH, respectively, $n = 3$ ($p < 0.05$). Increasing temperature also resulted in diminished aerosol performance. These differences were more marked for albuterol sulfate. The fine particle percent of the emitted dose of albuterol base was always greater than that of albuterol sulfate under similar environmental conditions. The reverse was true when fine particle percents of the loaded dose were considered because only $32 \pm 6.6\%$ of the loaded albuterol was emitted from the inhaler as compared to $58.5 \pm 6.3\%$ of albuterol sulfate (mean $\pm$ SD, $n = 27$). There is a need, in some circumstances, to define specific ranges of temperature and humidity for the testing of dry powder aerosols.

Keywords: Aerosol; Dry powder inhaler; Twin stage impinger; Environment; Humidity; Temperature; Albuterol; Albuterol sulfate; Pulmonary delivery; Powder inhalation; Salt

1. Introduction

There is currently considerable discussion concerning the establishment of compendial test methods suitable for dry powder inhalers (Hugosson et al., 1993). Even though it is likely that different inhalers will have to be tested at differ-

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SSDI 0378-5173(94)00197-9

ent flow rates (Spiro et al., 1992; Clark and Hollingworth, 1993) many companies and investigators (Hugosson et al., 1993) support the use of the BP/USP twin stage impinger for determination of the respirable or fine particle fraction discharged from dry powder inhalers at 60 l/min. Because humidity is known to affect aerosol size for hygroscopic compounds (Byron et al., 1977; Smith et al., 1980; Plomp et al., 1987; Hickey and Martonen, 1992), temperature changes induce changes in water activity at fixed absolute humidity, and a wide variety of environmental conditions exist under which dry powder inhalers will ultimately be used and tested, we have studied the influence of changing environments on the respirable characteristics of dry powder aerosols formed by deaggregation of micronized albuterol and albuterol sulfate in a model dry powder inhaler.

2. Materials and Methods

Micronized albuterol (Glaxo's ACN 58548) and albuterol sulfate (Glaxo's ACN 84530) were donated by Glaxo, Inc., Research Triangle Park, NC. Albuterol sulfate was further micronized using a jet mill (Model 00-Jet-O-Mizer, Fluid Energy Processing & Equipment Co., Hatfield, PA). The jet mill used 5 SCFM (0.14 m^3/min) of air compressed at 80 psig (653 kPa, absolute pressure) and room temperature. Albuterol sulfate was stored in a desiccator at room temperature and 1 atm pressure over Drierite (W.A. Hammond Drierite Co., Xenia, OH) whereas albuterol was stored in a tightly closed container at room humidity and temperature (14–67% RH, 17–24°C). Both powders were protected from light. Both micronized drugs were used pure and were not blended with excipients. Particle size distributions of the powders were determined using an Aerosizer®, equipped with AeroDisperser™ (Amherst Processing Instruments, Inc., Hadley, MA) and confirmed using light microscopy. Powders were examined under crossed polars (Optiphot, Nikon, Tokyo, Japan) to ascertain any macroscopic changes in crystallinity resulting from micronization procedures. Particle shape was determined by scanning electron microscopy (Joel JSM-820, Joel, Peabody, MA).

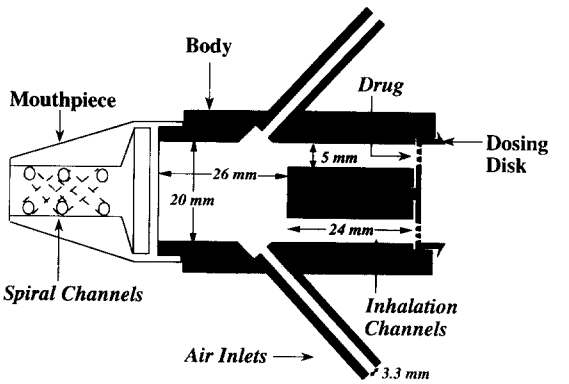

Fig. 1. Dry powder inhaler shown in the testing position. The stainless steel body of the inhaler was constructed to fit the dosing disk and mouthpiece from a marketed Turbuhaler® (Bricanyl®, Astra-Draco AB, Lund, Sweden). The internal diameter of the two air inlets was 3.3 mm and there were five cylindrical inhalation channels to correspond to the positions of the five metering stations on the dosing disk.

2.1. Description of the model dry powder inhaler

A model dry powder inhaler (DPI) was constructed with dimensions as shown in Fig. 1. The device utilized the plastic dosing disk and mouthpiece of a commercially available inhaler, Turbuhaler® (Bricanyl®, Astra-Draco AB, Lund, Sweden). The dosing disk had five dosing stations, each with six conical metering holes. In the Turbuhaler®, only one of these stations is used to meter and deliver drug down a single inhalation channel, at any given time. In this study however, five stations were used to meter > 1.7 mg into five inhalation channels on each occasion. In this way, it was possible to load the disk by hand and reduce the variations in the loaded dose to manageable levels. When air was pulled through the inhaler equipped with a drug-free dosing disk at 60 l/min, 33 l/min flowed through the dosing disk and 27 l/min entered through the two air inlets on the body of the device.

2.2. Twin stage impinger experiments

Detailed descriptions of the twin stage impinger (TSI) are available in the British (1988)

and US (1992) pharmacopoeias. The TSI used in this study was obtained from Copley Instruments Ltd, Nottingham, U.K. When operated at 60 l/min, stage 2 of the device is claimed to collect fine particles with aerodynamic diameters < 6.4 μm while larger material remains in stage 1 (Hallworth and Westmoreland, 1987). In many publications (Phillips et al., 1990; Hickey, 1992), drug penetrating stage 2 of the TSI is considered to be potentially 'respirable', although it is now more common to define a 'fine particle fraction' or 'fine particle dose' in the same way (Inhalanda, 1993).

The TSI was housed inside an environmental cabinet (Model 435314, Hotpack, Philadelphia, PA) and allowed to equilibrate for > 30 min at a set temperature and relative humidity (RH). Albuterol and albuterol sulfate were aerosolized and collected in triplicate experiments at different temperatures (20, 30, 45°C) and relative humidities (30–95% RH). Micronized pure drug powders were lightly scraped across the metering holes of the dosing disk using a spatula. Excess drug was discarded. The disk was then fitted to the inhaler (the latter had been pre-equilibrated at the testing temperature in a dry container) and the loaded inhaler inserted into the inlet of the TSI. The chamber was resealed and after 3 min, drug was aerosolized using a flow rate of 60 l/min for 20 s. Drug was collected from different parts of the dry powder inhaler and impinger by washing and dissolving in 0.01 N NaOH. Washings were analyzed by UV spectroscopy (Ultrospec II, LKB spectrophotometer, LKB Biochrom Ltd, Cambridge, U.K.) at 243 nm. The 3 min time interval between DPI loading and aerosolization was chosen to allow the cabinet to return to the assigned temperature and humidity after introduction of the inhaler. Albuterol was also tested using a 60 min time interval to test the effect of storage time on aerosol performance.

2.3. Statistical analyses

Statistical differences in aerosol performance and loaded dose of albuterol under any given environmental condition following either 3 or 60 min exposure were tested using the t-test at a level of significance of $\alpha = 0.05$, while assuming unequal variances. The various aspects of aerosol performance tested were the percent of loaded dose dislodged from the disk, percent of loaded dose emitted from the inhaler mouthpiece, fine particle dose, fine particle percent of loaded dose and fine particle percent of emitted aerosol. Scheffe's multiple comparison test was used to detect differences in loaded doses of the drug (either albuterol or albuterol sulfate) across all environmental conditions for the 3 min exposure experiments. Multiple regression analysis with absolute humidity and temperature as independent

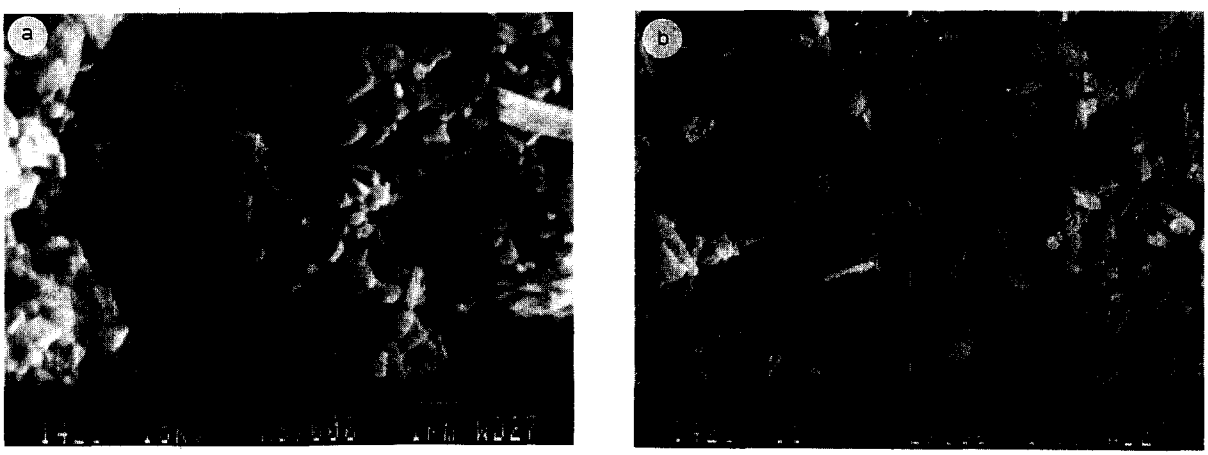

Fig. 2. Scanning electron micrographs of (a) albuterol at 8000 × magnification and (b) albuterol sulfate at 2000 × magnification.

variables and the various aerosol performance outcomes (defined above) as dependent variables gave indications as to the presence of any empirical relationships between the outcome variable and absolute humidity and temperature.

3. Results and discussion

3.1. Particle size distributions

Scanning electron micrographs (Fig. 2) showed that albuterol particles were isometric cuboids with axial ratios (Phillips et al., 1993) of 1.36 ± 0.41 (mean $\pm$ sample standard deviation (SD), $n = 26$) while albuterol sulfate particles had ratios of 2.5 ± 1.4 (mean $\pm$ sample SD, $n = 15$). The aerodynamic diameters of 100% albuterol and albuterol sulfate by mass were < 6.4 μm as determined using the Aerosizer®. and AeroDisperser™. The mass median aerodynamic diameters were 1.26 ± 0.05 and 2.12 ± 0.07 μm for albuterol and albuterol sulfate, respectively (mean $\pm$ sample SD, $n = 3$). Thus, both powders when completely deaggregated, could theoretically penetrate stage 2 of the TSI in their entirety. Both powders were highly crystalline when observed under crossed polars and the Aerosizer® results were consistent with microscopic observations. Even though micronization can increase the content of amorphous material (Phillips and Byron, 1994), there were no detectable changes in crystallinity resulting from milling.

3.2. Twin stage impinger experiments

During drug metering with a device like Turbuhaler®, air can be drawn both through the dosing disk and through the device's alternate air inlets (Jaegfeldt et al., 1987). When all the holes in the dosing disk are full, the likelihood of powder displacement at the onset of airflow is high. As holes empty, however, airflow takes the route of least resistance and it is possible that some holes in the dosing disk will fail to empty. There were no experiments in this study in which more than six metering holes (of 30) failed to empty, while in the majority of the experiments not more than four holes failed to empty. The dosing disk could be loaded with a precision reflected by an overall coefficient of variation of 14.4% ($n = 42$) for albuterol and 8% ($n = 27$) for

Table 1
Effect of varying temperature, humidity and storage time on the aerosol performance of albuterol powder from the model DPI (Fig. 1)

Condition			Results [a]			
Temperature (°C)	Humidity [a] (% RH)	Time (min)	Absolute dose (μg)	Percent in device (%)	Percent in stage 1 (%)	Percent in stage 2 (%)
20	48.5 (0.7)	3	2330 (251)	60.3 (7.6)	8.81 (0.6)	30.9 (7.3)
	49.7 (0.0)	60	2149 (202)	63.7 (2.5)	7.1 (1.4)	29.2 (3.5)
	80.9 (0.1)	3	2130 (717)	65.1 (13.4)	8.75 (4.7)	26.2 (8.7)
	79.7 (0.1)	60	2106 (460)	62.9 (6.5)	11.7 (6.3)	25.4 (3.2)
30	42.2 (3.1)	3	2564 (635)	69.2 (14.3)	7.7 (6.0)	23.1 (8.2)
	54.5 (1.5)	3	2628 (291)	66.4 (5.9)	9.2 (8.4)	24.4 (4.9)
	84.7 (0.9)	3	2615 (213)	72.4 (8.5)	10.1 (4.6)	17.5 (3.9)
45	30.6 (2.1)	3	1939 (307)	63.1 (3.8)	8 (0.7)	29.0 (3.8)
	29.8 (0.1)	60	1987 (811)	60.5 (14.4)	11.1 (8.9)	28.4 (5.5)
	53.7 (3.4)	3	1836 (243)	66.4 (7.8)	10.4 (5.5)	23.2 (2.3)
	49.7 (0.1)	60	2015 (256)	71.0 (17.3)	7.5 (6.6)	21.5 (11.0)
	80.6 (1.2)	3	2049 (432)	69.8 (3.6)	14.8 (2.5)	15.4 (3.1)
	79.7 (0.1)	60	2127 (298)	68.3 (15.6)	11.8 (7.9)	19.9 (7.8)
	92.7 (0.7)	3	2067 (314)	79.1 (11.4)	11.3 (7.6)	9.6 (3.8)

[a] Values are mean (experimental range), $n = 3$.

Table 2
Effect of varying temperature and humidity on the aerosol performance of albuterol sulfate powder from DPI

Conditions		Results [a]			
Temperature (°C)	Humidity [a] (% RH)	Absolute dose (μg)	Percent in device (%)	Percent in stage 1 (%)	Percent in stage 2 (%)
20	55.1 (0.9)	3225 (200)	40.1 (9.8)	21.8 (4.6)	38.1 (5.4)
	86.2 (1.8)	3154 (331)	49.0 (16.6)	21.4 (8.5)	29.6 (9.0)
30	43.1 (3.2)	3481 (622)	36.4 (11.7)	25.8 (6.0)	37.8 (7.1)
	55.0 (2.9)	3474 (929)	35.2 (7.8)	30.1 (5.6)	34.7 (6.7)
	84.6 (0.8)	3645 (324)	42.4 (16.2)	37.1 (12.9)	20.5 (4.6)
45	33.7 (1.2)	3390 (381)	43.5 (10.6)	18 (6.2)	38.5 (6.0)
	55.3 (0.7)	3385 (262)	41.0 (12.1)	29.0 (7.3)	30.0 (4.8)
	80.9 (0.4)	3070 (247)	43.8 (8.6)	37.9 (7.4)	18.3 (5.9)
	93.8 (0.4)	3363 (472)	42.4 (5.3)	47.4 (7.8)	10.2 (4.9)

[a] Values are mean (experimental range), $n = 3$.

albuterol sulfate. The mean amount of albuterol metered by the dosing disk was 2.2 mg while for albuterol sulfate it was 3.4 mg, reflecting the difference in bulk density of the two micronized powders.

Results from the TSI experiments were expressed as fine particle dose and fine particle percents. Fine particle dose was the amount collected in stage 2 of the TSI. This amount was also expressed as the fine particle percent of either the loaded dose or the amount emitted from the mouthpiece of the DPI.

Tables 1 and 2 summarize the distribution of albuterol and albuterol sulfate, respectively, after aerosolization following brief exposure to different temperatures and humidities. In the case of albuterol (Table 1) results are also presented following 60 min exposure to practically identical experimental conditions. The duration of exposure to a particular environment failed to produce a statistically significant difference ($\alpha = 0.05$) in aerosol performance in all cases with one exception. This exception was for the fine particle percent of the emitted dose of albuterol from the mouthpiece of the DPI at 45°C and nominal 80% RH (data in Table 1). The mean (experimental range) values of this mathematically transformed variable were 51.0 (7.6) and 63.5 (9.7)% after 3 and 60 min exposure, respectively. However, there was no significant difference in the percent collected in stage 2 of the TSI, when the two conditions were compared using the raw data presented in Table 1. It appeared that the performance changes induced by modification of RH and temperature occurred very quickly in the case of albuterol base. The effect of the 3–60 min

Table 3
Summary of doses

	Albuterol		Albuterol sulfate
	3 min [a]	60 min [b]	3 min [a]
Dose loaded in disk, μg	2240 ± 344	2080 ± 226	3350 ± 267
Amount dislodged from disk, μg	1430 ± 183	1330 ± 116	2520 ± 250
(mean %) [c]	(64.5)	(64.6)	(75.4)
Dose emitted from DPI mouthpiece, μg	710 ± 156	720 ± 135	1960 ± 266
(mean %) [c]	(32.0)	(34.7)	(58.5)

[a] Results are mean ± sample SD, $n = 27$.
[b] Results are mean ± sample SD, $n = 15$.
[c] Numbers in parentheses are the corresponding mean percentages of the dose loaded in disk.

exposure on albuterol sulfate was not determined.

A greater percentage of albuterol sulfate left the device than albuterol base (Tables 1 and 2, all cases), possibly reflecting the smaller, and more adhesive, particle size distribution for albuterol compared to its sulfate salt (mass median aerodynamic diameters = 1.3 and 2.1 μm, respectively). However, when results for percent of loaded dose emitted from the mouthpiece were reviewed as functions of temperature and absolute humidity, there were no trends as observed from multiple linear regression analysis (percent of loaded dose emitted from the mouthpiece was the dependent variable and temperature and absolute humidity were the independent variables). This was also the case for percent of loaded dose which emptied from the dosing disk (percent of loaded dose which emptied from the disk was the dependent variable and temperature and absolute humidity were the independent variables). Coefficients of correlation (r^2) were between 0.01 and 0.4. In addition, Scheffe's multiple comparison test showed no significant differences in the total dose of albuterol or albuterol sulfate loaded in the inhaler. Accordingly, Table 3 shows the variation in the loading and emptying of the dosing disk as well as the emitted dose over all of the conditions studied. The variability observed in emitted doses and emitted percents of loaded doses was consistent with that obtained for commercially available dry powder inhalers (Hindle and Byron, 1993).

Significant changes occurred in the fine particle dose and the fine particle percent of the emitted and metered dose when temperature and relative humidity were varied. While individual results are shown in Tables 1 and 2 a consistent trend emerged which is illustrated in Fig. 3. Increasing RH decreased the fine particle percent for both drugs. Similarly, increasing temperature at any given humidity produced the same effect, perhaps because of an increasing absolute humidity (mass water/mass air) as 'dry bulb' temperature is increased and relative humidity is held constant (Felder and Rousseau, 1986). Multiple linear regression analysis where fine particle dose and percents were viewed as functions of absolute humidity and temperature gave correlation coefficients (r^2) between 0.71 and 0.89. Results in Fig. 3 are presented as fine particle percent of dose emitted from the mouthpiece of the DPI. These results were numerically smaller when they were presented as fine particle percent of the dose loaded onto the disk (Tables 1 and 2). However, the trends were identical. Clearly, in cases like the Turbuhaler® where drug is metered from a bulk reservoir, the exact metered

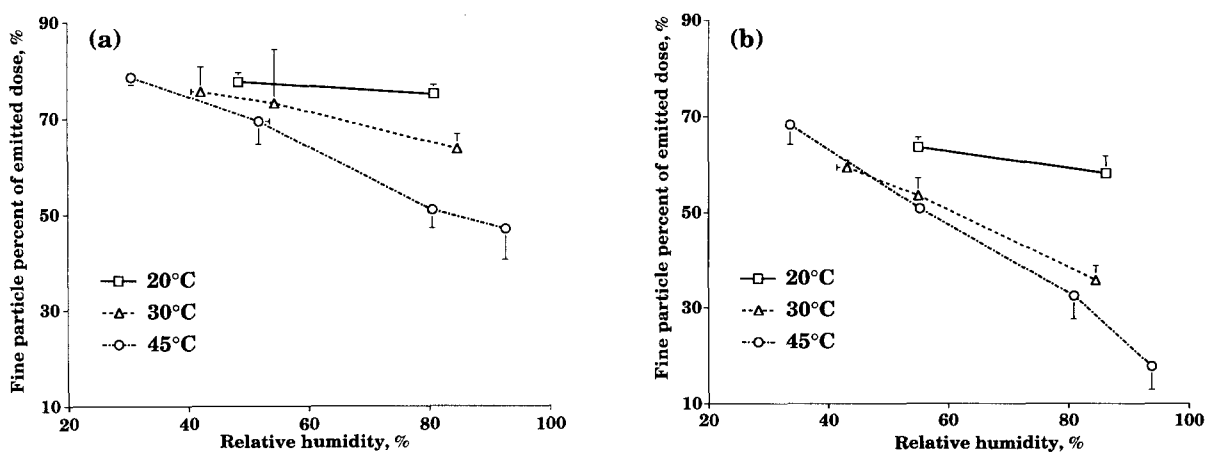

Fig. 3. Effect of a short (3 min) exposure to different relative humidities on the fine particle fraction of the emitted dose of (a) albuterol and (b) albuterol sulfate aerosols at 20 (□), 30 (△) and 45°C (○). Error bars show sample standard deviations.

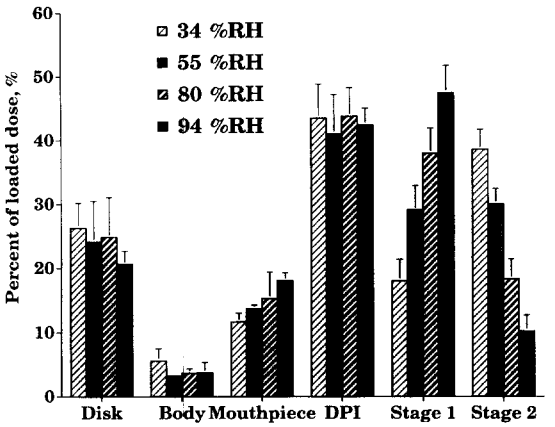

Fig. 4. Distribution of the initial loaded dose of albuterol sulfate following aerosolization for 20 s at 60 l/min, 45°C and four different relative humidities.

dose in a test situation is unknown and therefore data presentation in a way similar to that shown in Fig. 3 is inevitable.

Fig. 4 shows the drug distribution of albuterol sulfate at 45°C following aerosolization at four separate relative humidities. Fig. 4 illustrates a consistent trend which occurred in this study. As the fine particle percent decreased (increasing RH), mouthpiece retention increased only slightly and retention was not significantly altered in the remainder of the DPI. Thus, the emitted dose was left largely unchanged, while varying RH and drug deposition in stage 1 of the TSI increased as the fine particle percent decreased. Some experiments performed on albuterol sulfate in the absence of the spiral channels in the DPI mouthpiece (Fig. 1) showed the importance of these channels to the powder deaggregation process (Jaegfeldt et al., 1987). Less than 1.5% of the dose ever penetrated stage 2 of the TSI in the absence of the mouthpiece, under any conditions of RH and temperature tested. At 45°C and 95% RH, only 0.11% of the loaded dose penetrated stage 2 when the mouthpiece was omitted.

Both particle deaggregation and hygroscopic particle growth (Byron et al., 1977; Plomp et al., 1987) may be affected by the changing conditions of temperature and humidity employed in this study. Furthermore, it is extremely difficult to determine the relative importance of these effects in studies of this kind, especially given the differences in size and shape between the two micronized powders (contact and packing of the salt crystals appeared to be worse than that of the free base which was smaller and more uniform in size; Fig. 2). In the practical case, where the fine particle percent of the dose from a DPI must be determined, however, the mechanisms where humidity and temperature affect DPI output are unimportant. The bigger issues concern: (a) the avoidance of temperature and humidity effects via formulation and suitable salt selection; (b) if necessary, the definition of an acceptable range of temperature and humidity under which the more important variable, the fine particle dose, should be determined and also, if necessary; (c) the selection of suitable exclusion conditions under which a patient should be advised that device performance and therapeutic effect may be impaired. The avoidance of temperature and humidity effects via suitable salt selection and/or formulation will be the subject of a future publication. Clearly, the selection of an acceptable range of temperature and humidity with which to perform quality control testing of a given DPI will be dependent both on formulation and device, and should also relate to the number of experimental determinations to be performed and the dosing variability seen under fixed temperature and humidity conditions. In short, the test and the conditions under which it is performed need to be validated. The most difficult subject to address – the conditions under which a product may lose its efficacy and should not be used is probably too difficult to resolve. Thus, formulators and DPI designers should aim to avoid the large variations seen in fine particle dose and fine particle fraction in this paper with pure micronized albuterol and albuterol sulfate.

Acknowledgements

R.N.J. acknowledges partial support from the USP Convention in the form of a fellowship. The authors thank Glaxo, Inc. for donating albuterol and albuterol sulfate. The authors also wish to

thank Dr Jürgen Venitz, Virginia Commonwealth University, for helpful comments and suggestions regarding the statistical analysis of the data.

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