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Dry powder aerosol generation in different environments: performance comparisons of albuterol, albuterol sulfate, albuterol adipate and albuterol stearate

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Abstract

Aerosols formed by three salts and the free base of albuterol were compared following their formation from similarly micronized crystalline powders held in a model dry powder inhaler (DPI) under varying environmental conditions. Aqueous solubility at 22°C was the greatest for albuterol adipate diethanolate (353 mg/ml), followed by albuterol sulfate (250 mg/ml), albuterol free base (15.7 mg/ml) and albuterol stearate (0.6 mg/ml). Temperature and relative humidity (RH) of the air drawn through the inhaler was systematically varied in the range 20–45°C and 30–95% RH. Several inhaler performance outcomes were compared statistically between physical forms and across the applied environmental conditions. Significant differences ($P < 0.05$) existed between powder forms with respect to emptying of the metering disk, inhaler emptying, powder deaggregation, fine particle dose (mass < 6.4 μm aerodynamic diameter), and each compound's susceptibility to temperature and relative humidity. The free base emptied poorly from the inhaler compared to all salt forms. Inhaler emptying for all four compounds was unaffected by temperature and humidity over most environments tested ($P > 0.05$) although only albuterol adipate diethanolate and albuterol sulfate were insensitive at 94% RH and 45°C. At 20°C and 50% RH, the fine particle percent of the emitted doses [mean (experimental range)] were 77.7 (7.3)%, 63.6 (4.2)%, 9.0 (1.8)% and 55.7 (3.4)% for the free base, sulfate, adipate diethanolate and stearate salts of albuterol, respectively. Fine particle doses and percents of albuterol and albuterol sulfate decreased progressively with increasing relative humidity and temperature while albuterol adipate diethanolate and albuterol stearate aerosol performance remained largely unaffected; these latter salts showed changes in fine particle percents only at 45°C and 95% RH although the adipate diethanolate deaggregated very poorly under all conditions. Overall, albuterol stearate, the most hydrophobic salt, emptied and aerosolized best from the inhaler and showed least sensitivity to temperature and humidity. Neither solubility nor moisture sorption correlated directly with inhaler performance in high humidity environments, showing that the multiplicity of factors controlling the quality of the emitted aerosol from DPIs prevents straightforward prediction of optimal physical forms and mandates their experimental review. Nevertheless, salt selection is an important area to screen as new compounds are developed for inhalation and DPI device performance continues to improve.

Keywords: Aerosols; Powder inhalation; Albuterol; Salts; Humidity; Temperature; Dry powder inhalers; Twin stage impinger

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1. Introduction

Environmental conditions (temperature, humidity) may adversely affect aerosol generation and the particle size distributions from dry powder inhalers (DPIs), either by modifying adhesive or cohesive properties of the formulation or by inducing hygroscopic growth (Hindle et al., 1994; Jashnani et al., 1995). Hygroscopic growth occurs when aerosol particles sorb moisture; at relative humidities > the critical relative humidity, CRH, they dissolve to form saturated solution droplets, which continue to grow and become more dilute if the humidity of the surroundings is greater than the humidity to be found over the saturated solution of the compound (Orr et al., 1958). Theoretically, CRH may be used to rank compounds with respect to hygroscopicity (smaller values indicate larger hygroscopicities); theoretical CRH may be estimated from the ratio of the vapor pressure present over the planar surface of the saturated solution of the compound to the vapor pressure of pure water as a planar surface at the same temperature. This ratio is multiplied by 100 to be expressed as a percentage. In this paper, albuterol stearate had the lowest solubility (Jashnani et al., 1993) and the greatest theoretical CRH.

Water sorption can also affect the magnitude of cohesive forces (between micronized powder particles) and adhesive forces (between particles and DPI surfaces) at humidities < CRH. Even if issues of solid state physical stability (Otsuka et al., 1991) are neglected, interparticulate forces may increase in the presence of moisture (Corn, 1966, Shatton and Harb, 1966, Fukuoka et al., 1983, Heng and Staniforth, 1988), resulting in alterations in flow characteristics and the ease with which the powder can deaggregate during aerosolization. For example, powder aerosols of both, hygroscopic sodium cromoglycate (Bruna et al., 1994, Byron et al., 1977, Smith et al., 1980) and nonhygroscopic terbutaline sulfate (Bruna et al., 1994, Wetterlin, 1988) show reduced fine particle fractions when exposed to elevated temperatures and humidities. These facts have been attributed to the tendency of sodium cromoglycate to sorb moisture (Cox et al., 1971) and to the hardening of terbutaline sulfate aggregates when exposed to moisture (Wetterlin, 1988).

Thus, it may be possible to optimize dry powder aerosol formulations by selecting environmentally-insensitive salt forms with reduced hygroscopicities (Jashnani et al., 1995). This would have several obvious advantages: extensive DPI testing in field environments could be avoided, routine batch release testing would not require strictly controlled conditions and, importantly, there would be no need to advise patients to take precautions when using their DPIs in certain environments. The purpose of this paper was thus to test two novel micronized salts of albuterol, albuterol adipate diethanolate and albuterol stearate (Jashnani et al., 1993) in a model DPI in varying environments; then to compare their aerosol behavior to that of the commercially available albuterol free base and albuterol sulfate under identical conditions, as described earlier (Jashnani et al., 1995).

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 adipate diethanolate and albuterol stearate were prepared and characterized as described previously (Jashnani et al., 1993). The sulfate, adipate and stearate salts were micronized (Model 00-Jet-O-Mizer, Fluid Energy Processing and Equipment Company, Hatfield, PA), as described previously (Jashnani et al., 1995). Infrared spectra and thermal behavior were confirmed (Jashnani et al., 1993) after micronization. Salts were stored in a desiccator over Drierite (W.A. Hammond Drierite Company, Xenia, OH) at room temperature. Albuterol base was stored in a well sealed container, held at room humidity and temperature (14–67% RH, 17-24°C). All four powders were protected from light and tested pure (unblended with excipients). Chemical structures are shown in Fig. 1.

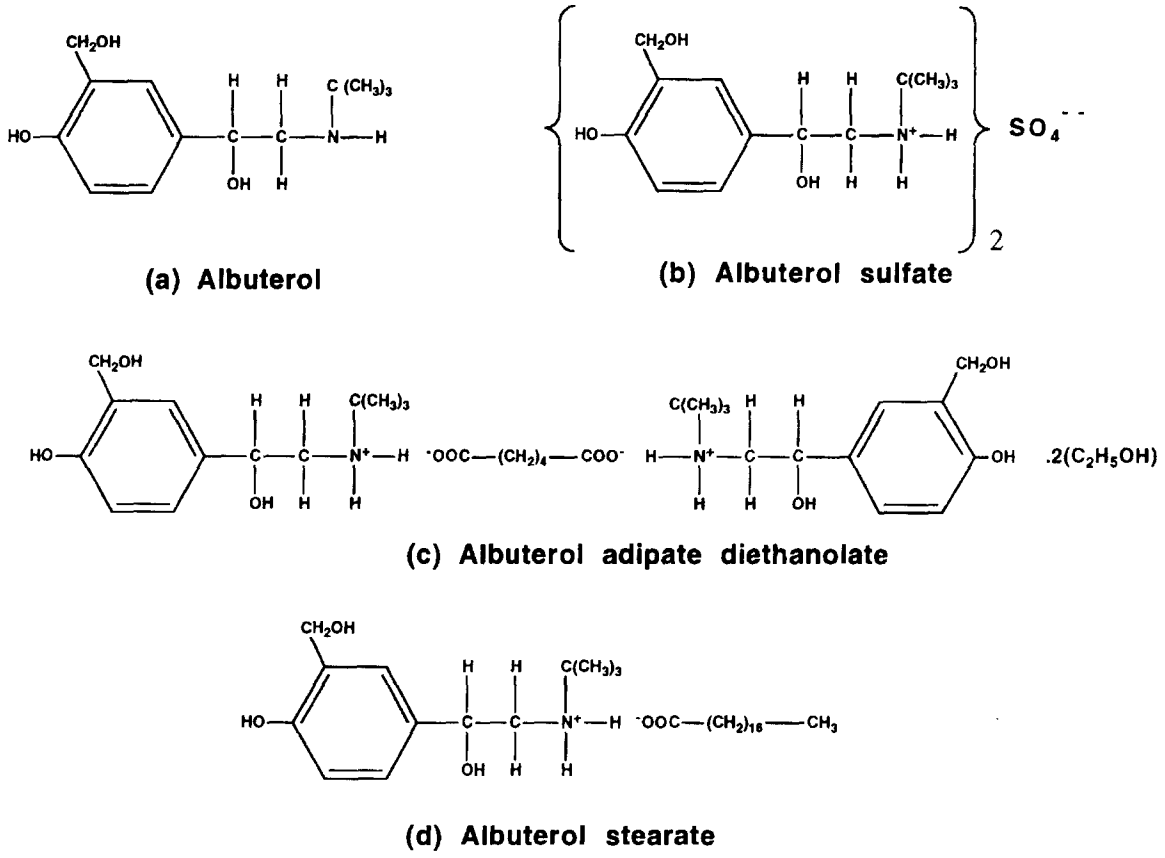


Fig. 1. Chemical structure of (a) albuterol, (b) albuterol sulfate, (c) albuterol adipate diethanolate and (d) albuterol stearate.

2.1. Particle characteristics

Particle size distributions were determined using Aerosizer® with AeroDisperser™ (Amherst Processing Instruments, Inc., Hadley, MA) and confirmed using light microscopy (Hindle and Byron, 1995a). Particle morphology was investigated using scanning electron microscopy (SEM, Joel JSM-820, Joel, Peabody, MA). Powder was mounted onto metal stubs with transfer tape (double sided sticky tape) and coated with gold using an Eiko IB-2 Ion Coater (Eiko Engineering, Ibaraki, Japan). True particle density (required for Aerosizer®) was measured by helium pycnometry (AccuPyc 1330 Gas Pycnometer, Micromeritics, Norcross, GA), performed at Micromeritics Materials Analysis Laboratories, Norcross, GA. Outgassing temperatures of the samples were controlled between 25.4°C and 27.5°C. Equilibrium moisture sorption of each physical form (previously dried to constant weight at 60°C) was studied from 0 to 95% RH at 25°C using a VTI Moisture Sorption Meter (Model MB-300, VTI Corporation, Hialeah, FL) at Hoffmann La-Roche, Nutley, NJ.

2.2. Twin stage impinger experiments

Micronized pure drug was loaded into a model dry powder inhaler (Fig. 2) and aerosol perfor-

mance tested in a twin stage impinger (TSI, Copley Instruments Ltd., Nottingham, U.K.), exactly as described previously (Jashnani et al., 1995). Briefly, the DPI utilized the plastic dosing disk and mouthpiece of a commercially available inhaler, Turbuhaler® (Bricanyl®, Astra-Draco AB, Lund, Sweden), connected to a stainless steel body into which dilution air was drawn through two side ports. In the absence of a powder charge in the disk, when 60 L/min airflow was drawn through the inhaler, 27 L/min flowed through the side ports and 33 L/min flowed through the combined holes in the dosing disk. The TSI was equilibrated at a specific temperature and humidity for 30 min in an environmental chamber (Model 435314, Hotpack, Philadelphia, PA). The temperature-equilibrated DPI, containing its 'dosing disk' loaded with micronized powder (Fig. 2; Jashnani et al., 1995) was inserted into the inlet of the TSI and the environmental chamber resealed. Three min re-equilibration was allowed [to bring the chamber back to test condition; (Jashnani et al., 1995)] and the DPI tested by withdrawing air at 60 L/min for 20 s through the TSI. The drug powder was collected from different parts of the DPI and TSI by washing and dissolving in either 0.01 N NaOH (albuterol free base, albuterol sulfate and albuterol adipate diethanolate) or methanol (albuterol stearate). Washings were analyzed by UV spectroscopy (Ultrospec II, LKB spectrophotometer, LKB Biochrom Ltd., Cambridge, England, U.K.) at 243 nm (0.01 N NaOH) or 278 nm (methanol). Experiments were performed in triplicate at each pair of environmental condition (20, 30 or 45°C; 30–95% RH).

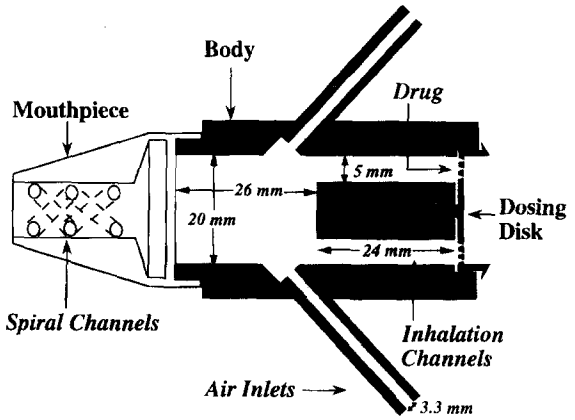
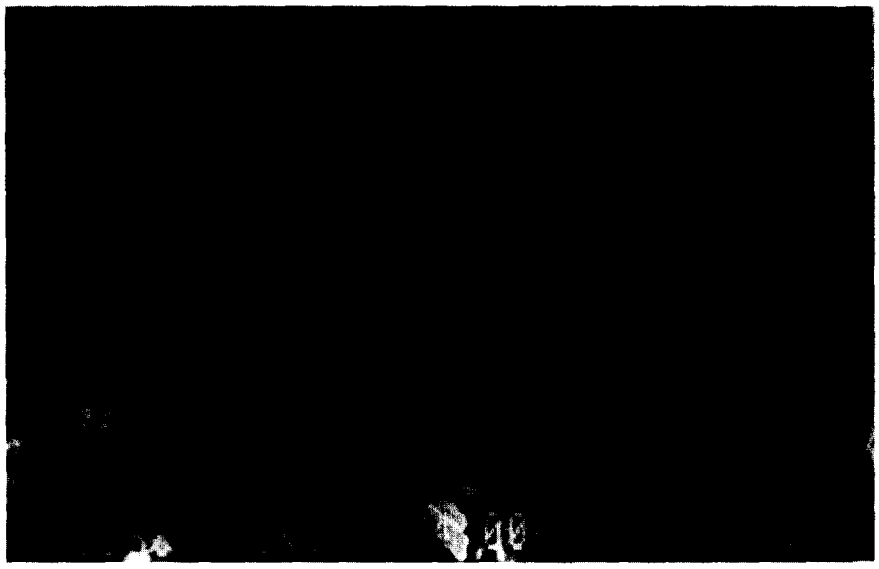


Fig. 2. Model dry powder inhaler (DPI) shown in the horizontal testing position. The stainless steel body of the inhaler was constructed to fit the dosing disk and mouthpiece of the marketed Turbuhaler® (Bricanyl®, Astra-Draco AB, Sweden). All dimensions were as shown with the internal diameter of the two air inlets = 3.3 mm; there were five cylindrical inhalation channels to correspond to the positions of the five metering stations on the dosing disk.

2.3. Statistical analyses

All statistical analyses were performed at a level of significance of $\alpha = 0.05$, while ensuring normality of resulting residuals. To ensure consistency in metering (or loading) of drug into the disk between experiments, Scheffe's multiple comparison tests were performed on groups of loaded doses determined and tested across the different environments studied. Aerosol performance outcomes tested were 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 or fine particle percent of emitted dose. The last three variables were defined as amount collected in stage 2 of the TSI, (amount in stage 2)/(loaded dose) and (amount in stage 2)/(emitted dose), respectively. Multiple regression analyses were also performed with absolute humidity (kg water/kg dry air) and temperature (°C) as independent variables and aerosol performance outcomes (defined above) as dependent variables in order to search for relationships between the outcome variable and environment. To ensure normality of the residuals, fine particle dose and percents of albuterol adipate diethanolate (dependent variables) were log-transformed and multiple regression analyses results presented for the log-transformed variables. Coefficients of determination were used to assign the proportion of total variability in the dependent variable, which was apparently due to each independent variable. Scheffe's multiple comparison test was also used to detect significant differences in

a



b

Fig. 3. Scanning electron micrographs of (a) micronized albuterol adipate diethanolate and (b) micronized albuterol stearate. SEMs of albuterol base and albuterol sulfate were shown in Jashnani et al., 1995.

Table 1
Particle size, morphology and density

	Albuterol free base	Albuterol sulfate	Albuterol adipate diethanolate	Albuterol sterate
Axial ratio[a] using SEM[b]	1.4 ± 0.4 (n = 26)	2.5 ± 1.4 (n = 15)	1.2 ± 0.2 (n = 9)	1.4 ± 0.6 (n = 10)
% mass < 6.3 μm aerodynamic diameter using Aerosizer®	100%	100%	96%	99%
MMAD[c] using Aerosizer®, μm[b]	1.26 ± 0.05	2.12 ± 0.07	3.46 ± 0.18	3.64 ± 0.24
True density by helium pycnometry, g/cm^3	1.15	1.34	1.22	1.07

[a]Axial ratio = longest length of particle/longest width of particle (Phillips et al., 1993).
[b]Numbers are mean ± sample standard deviation.
[c]MMAD is mass median aerodynamic diameter.

loaded doses and aerosol performance outcomes (defined above) for experiments performed at 20°C (50 and 80% RH) and 30°C (40, 50 and 80% RH).

3. Results and discussion

3.1. Physical characteristics

Methods of salt preparation and characterization (scanning calorimetry, infrared spectra, elemental analyses, aqueous solubilities in water and buffers, and intrinsic dissolution rates) have been reported previously (Jashnani et al., 1993). The micronized albuterol and albuterol sulfate batches used in an earlier publication were identical to those described here (see SEMs in Jashnani et al., 1995); SEMs of the adipate ethanolate and stearate salts are shown in Fig. 3. Table 1 and Fig. 4 summarize all particle characteristics, aerodynamic size distributions and true densities of each of the four physical forms as they were used. Each compound had at least 96% of its mass < 6.3 μm in aerodynamic diameter (Aerosizer® with AeroDisperser®) and thus, > 96% of each powder, if completely deaggregated by the model DPI, could theoretically penetrate stage 2 of the TSI (Hallworth and Westmoreland, 1987). All powders were highly crystalline when observed under crossed polars, although shapes and axial ratios differed between salts (Table 1). There was no evidence of thermodynamic instability of any of the physical forms stored over dessicant. Table 2 summarizes the results from moisture sorption experiments. Only albuterol sulfate showed a critical relative humidity (CRH) in the RH = 0 through RH = 95% range investigated; at RH > 93.5%, its weight increased rapidly and it dissolved in sorbed water (probably indicating some amor-

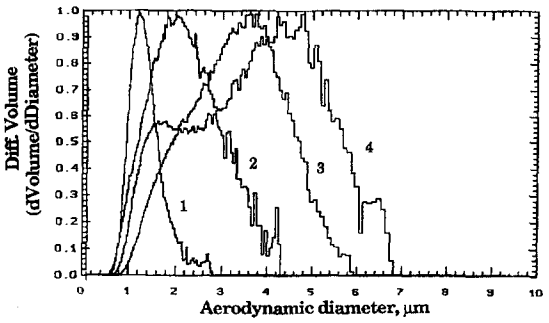


Fig. 4. Particle size distributions between 0–10 μm aerodynamic diameter of albuterol free base (1), albuterol sulfate (2), albuterol adipate diethanolate (3) and albuterol stearate (4) as determined using Aerosizer® with AeroDisperser® expressed as distribution by particle volume. Curves were normalized so that the peak value in each distribution = 1.0 (Hindle and Byron, 1995a).

Table 2
Results of equilibrium moisture sorption studies at 25°C

Physical form	Weight change (%)[a] at relative humidities (% RH)					Critical relative humidity (% RH)
	20	50	60	80	95	
Albuterol free base	0.06	0.19	0.25	0.40	0.60	NA[b]
Albuterol sulfate	0.15	0.36	0.41	0.46	0.71	93.5
Albuterol adipate diethanolate	1.11	1.67	1.61	-2.78	-4.05	NA[b,c]
Albuterol stearate	0.01	0.12	0.16	0.26	0.40	NA[b]

[a]Percentage weight gain/loss from that of the material dried at 60°C for 1 h. Positive numbers denote weight gain. Negative numbers denote weight loss.
[b]Not available. No criticality (sharp increase in weight at a particular relative humidity) was observed in the humidity rangetested.
[c]At RH > 60 %, ethanol was gradually displaced from the crystal structure.

Table 3
Effect of varying temperature and humidity on the aerosol performance of micronized albuterol adipate diethanolate

Conditions		Results[a]			
Temp. °C	Humidity[a] %RH	Loaded dose μg	Percent in DPI %[c]	Percent in stage 1[b] %[c]	Percent in stage 2[b] %[c]
20	51.1 (1.8)	2851 (328)	35.5 (8.3)	58.7 (8.7)	5.8 (0.5)
	81.2 (0.6)	3030 (299)	34.3 (15.3)	58.9 (21.4)	6.7 (7.6)
30	41.0 (0.8)	2920 (1002)	37.9 (20.7)	56.3 (20.7)	5.8 (0.2)
	52.1 (2.4)	3014 (823)	31.4 (29.9)	61.7 (31.9)	6.9 (2.1)
	84.3 (0.1)	2755 (778)	33.1 (5.4)	61.3 (4.7)	5.6 (2.1)
45	34.1 (1.8)	3073 (229)	32.9 (17.4)	59.1 (17.3)	8 (1.4)
	55.5 (0.9)	3111 (687)	33.2 (14.2)	59.3 (14.7)	7.4 (0.5)
	81.3 (0.1)	3228 (35.5)	31.6 (6.7)	63.3 (6.2)	5.0 (0.6)
	94.3 (0.6)	2826 (404)	31.7 (10.9)	66.6 (10.2)	1.7 (0.8)

[a]Values are mean (experimental range), $n = 3$.
[b]Stage 1 and stage 2 refer to the stages of the twin stage impinger. Stage 2 deposition indicates aerodynamic diameters < 6.4 micrometers (Hallworth and Westmoreland, 1987).
[c]Results are percent of loaded dose.

phous content in the milled product). Theoretical estimates of CRH increased with decreasing molar solubilities (Jashnani et al., 1993) and were 95.60, 97.67, 99.88 and 99.99% for the adipate, sulfate, free base and stearate forms of albuterol. Thus, theoretical hygroscopicity also ranked adipate > sulfate > base > stearate. The free base and the stearate showed small but steady weight gains with increasing RH (Table 2), as expected. Although albuterol adipate diethanolate retained ethanol until temperatures ≥ 120°C, under dry differential scanning calorimetry conditions, (Jashnani et al., 1993), it was metastable at RH > 60 % where it began to desolvate slowly with time (Table 2; in sorption experiments, the sample chamber was evacuated, then RH was

Table 4
Effect of varying temperature and humidity on the aerosol performance of micronized albuterol stearate

Conditions		Results[a]			
Temp. °C	Humidity[a] %RH	Loaded dose μg	Percent in DPI %[c]	Percent in stage 1[b] %[c]	Percent in stage 2[b] %[c]
20	54.8 (0.6)	2390 (161)	32.8 (0.9)	29.7 (1.9)	37.6 (2.8)
	87.4 (1.8)	2528 (302)	37.4 (7.8)	27.4 (5.5)	35.1 (2.5)
30	43.2 (0.5)	2733 (658)	38.7 (8.2)	25.7 (3.7)	35.6 (5.0)
	56.1 (1.7)	2554 (235)	34.2 (4.4)	29.4 (6.7)	36.4 (4.1)
	87.2 (1.0)	2787 (327)	39.2 (5.2)	26.7 (3.7)	34.1 (2.0)
45	32.4 (1.5)	2690 (297)	37.8 (3.5)	24.2 (2.6)	38.0 (5.3)
	55.9 (1.2)	2528 (277)	35.9 (7.3)	26.6 (7.8)	37.5 (4.0)
	81.4 (0.6)	2671 (413)	37.5 (4.3)	29.8 (1.4)	32.8 (2.9)
	94.2 (0.8)	2554 (275)	45.0 (13.4)	26.2 (8.9)	28.8 (4.5)

[a]Values are mean (experimental range), $n = 3$.
[b]Stage 1 and stage 2 refer to the stages of the twin stage impinger. Stage 2 deposition indicates aerodynamic diameters < 6.4 micrometers (Hallworth and Westmoreland, 1987).
[c]Results are percent of loaded dose.

Table 5
Summary of doses and emission behavior across all conditions tested (mean ± sample standard deviation, n = 27)

	Albuterol	Albuterol sulfate	Albuterol adipate diethanolate	Albuterol stearate
Dose loaded in disk (μg)	2240 ± 344	3350 ± 267	2980 ± 292	2600 ± 199
Amount dislodged from disk-μg	1430 ± 183	2520 ± 250	2190 ± 258	2200 ± 147
(Mean %)[a]	(64.5)	(75.4)	(73.8)	(84.8)
Dose emittedfrom DPI (μg)	710 ± 156	1960 ± 266	1970 ± 244	1650 ± 135
(Mean %)[a]	(32)	(58.5)	(66.5)	(62.4)

[a]Numbers in parenthesis are the corresponding mean percentages of the dose loaded in disk.

increased to 95% over 18 h). Within a commercial dry powder inhaler program, this fact alone may prevent further development of the adipate diethanolate. Furthermore, in the high RH (> 60%) aerosol experiments discussed below, slight desolvation of this salt cannot be precluded. However, because salts were exposed to each testing environment for 3 min only, prior to aerosolization, ethanol loss from this solvate was probably insignificant in all cases investigated.

3.2. Twin stage impinger experiments

3.2.1. Disk and inhaler loading and emptying

The data summarizing the distribution of albuterol adipate diethanolate and albuterol stearate before and after aerosolization in different environments is presented in Table 3 and Table 4. The data for albuterol and albuterol sulfate has been presented previously (Jashnani et al., 1995) and will only be abstracted here for

Table 6
Results of multiple linear regression analysis. [Model: y = (m × absolute humidity) + (n × temperature) + intercept + residual]

Dependent variable	Results[a]											
	Albuterol free base			Albuterol sulfate			Albuterol adipate diethanolate			Albuterolstearate		
y	r^2	m[b]	n[c]	r^2	m[b]	n[c]	r^2	m[b]	n[c]	r^2	m[b]	n[c]
Percent of loaded dose emitted from the DPI	0.4	-331	0.19	0.02	-47.8	-0.01	0.03	56	0.03	0.24	-151	0.04
		(99)	(0.16)		(125)	(0.18)		(142)	(0.23)		(76)	(0.12)
Percent of loaded dose dislodged from the disk	0.16	56.4	0.18	0.02	74.6	-0.04	0.19	119	0.12	0.02	36	-0.03
		(119)	(0.19)		(123)	(0.18)		(128)	(0.21)		(52)	(0.08)
Fine particle dose	0.88	-9630	1.28	0.83	-26900	18.2	0.53[f]	-15.3	0.02	0.56	-6660	7.58
		(1090)[d]	(1.76)[e]		(2770)[d]	(4.04)[e]		(3.01)[df]	(0.01)[ef]		(1220)[d]	(1.96)[e]
Fine particle percent of loaded dose	0.71	-462	0.26	0.80	-769	0.49	0.58[f]	-14.8	0.01	0.59	-226	0.2
		(72)	(0.12)		(90)	(0.13)		(2.68)[f]	(0.00)[f]		(41)	(0.06)
Fine particle pecent of emitted dose	0.83	-853	0.46	0.85	-1300	0.87	0.56[f]	-15.3	0.01	0.49	-230	0.29
		(97)	(0.16)		(126)	(0.18)		(2.92)[f]	(0.01)[f]		(48)	(0.08)

[a]Results are expressed as r^2 = coefficient of determination, m = partial slope for absolute humidity, n = partial slope for temperature. Numbers in parenthesis are the standard errors of the partial slopes, m and n.
[b]Units are [(kg dry air).(kg water)$^{-1}$.%] for all partial slopes (m), except for fine particle dose ('d' below).
[c]Units are [(°C)$^{-1}$.%] for all partial slopes (n), except for fine particle dose ('e' below).
[d]Units are [(kg dry air) (kg water)$^{-1}$.μg].
[e]Units are [(°C)$^{-1}$.μg].
[f]Dependent variable was log-transformed and results are presented for the log-transformed variable.

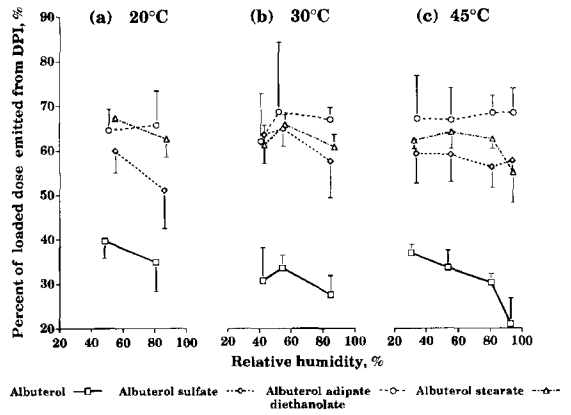


Fig. 5. Percent of loaded dose emitted from the DPI versus relative humidity at (a) 20°C, (b) 30°C and (c) 45°C. Error bars are sample standard deviations. Lines are drawn connecting points for the purposes of clarity only; data continuity is not implied.

comparative purposes. The dosing disk could be loaded with a precision reflected by relative standard deviations (RSDs) of 14.4% (n = 42), 8% (n = 27), 9.8% (n = 27) and 7.7% (n = 27) for the base, the sulfate, the adipate diethanolate and the stearate, respectively. Differences between salts in the mean amounts metered by the disk were reflections of differences in bulk density between micronized forms of the drug (Jashnani et al., 1995 and Fig. 3). Nevertheless, disk loading was consistent for each form of al

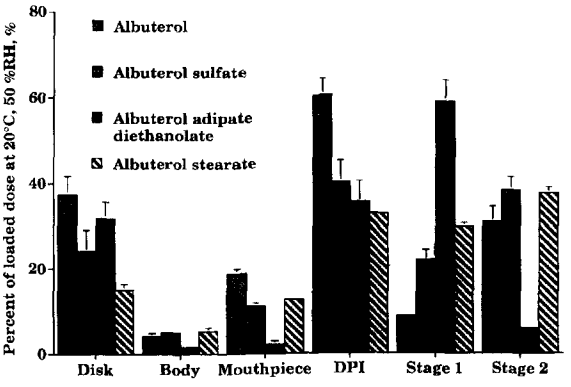


Fig. 6. Distribution of loaded dose of the four physical forms in various components of the model DPI and TSI at 20°C and ~50% RH. Error bars are sample standard deviations.

buterol when a form was tested across all experimental conditions ($P > 0.05$).

The mean amounts loaded and dislodged from the dosing disk and DPI are presented ($\pm$ sample standard deviation) across all conditions tested for all physical forms of the drug in Table 5. The variability observed in emitted doses and emitted percents of loaded doses from the DPI was consistent with that obtained for commercially available dry powder inhalers (Hindle et al., 1994, Hindle and Byron, 1995b). Furthermore, when disk emptying was reviewed for dependency on humidity and temperature by multiple linear regression analysis, coefficients of determination were consistently low (Table 6, row 2; $r^2 \leqslant 0.19$; thus, disk emptying was consistent across test conditions). Inhaler emptying (Table 6, row 1) was statistically independent of test conditions with two exceptions at the high extremes of RH and temperature. At 45°C and ~95% RH, the percent of loaded dose emitted from the DPI for albuterol and albuterol stearate only, decreased sharply (and significantly) from their values at 20°C and ~50% RH (Fig. 5). In all other cases (Fig. 5, Table 6), DPI emission as a percentage of loaded dose appeared to be independent of humidity and temperature.

All salts of albuterol emptied better from the DPI than the free base (Fig. 5). The adipate diethanolate and stearate were significantly better than the sulfate in this respect under many conditions although statistical significance was dependent on the test environment. These differences are best interpreted directly from Fig. 5 where overlapping error bars are a clear indication of insignificant differences. At 45°C and ~80% RH, for example, the percentage of the loaded dose emitted from the inhaler differed significantly between albuterol sulfate and the adipate diethanolate, while there was no difference between the same salts at 30°C and ~40% RH. Greatest variability in inhaler emptying was seen with the adipate diethanolate [RSDs of the dependent variable in Fig. 5 ranged from 4.1% at 30°C and 84% RH to 22.7% at 30°C and 52% RH]. RSDs for

emptying over all conditions were consistently smallest for albuterol stearate (Fig. 5 and Table 5).

3.2.2. Dose distribution after inhaler actuation

Fig. 6 shows the distribution of the loaded doses of the four compounds in the various components of the DPI and TSI following aerosolization in commonly accepted ambient conditions [20°C and 50–55% RH]. The major between-salt differences shown in this figure were typical of all other conditions. Albuterol free base was retained maximally in the DPI (disk + body + mouthpiece). Drug retention in the body of the DPI was small for all compounds; retention occurred mainly on the disk and the spiral channels of the mouthpiece. While it was possible to theorize about the between-salt differences in cohesive and adhesive properties affecting retention in and on different inhaler components, the arguments quickly became futile because of the multiplicity of variables involved [salt form, crystal size and shape, surface electronic charge (Staniforth, 1994, Jashnani et al., 1995)].

Although all the results may be influenced by hygroscopic growth (Morrow, 1986), deaggregation of the powder by the inhaler was believed to be the primary determinant of aerosol performance as measured in these experiments by stage 2 deposition in the TSI (fine particle dose). Removal of the spiral channels in the mouthpiece of the DPI resulted in large decreases in the fine particle dose to < 5.8% of the loaded dose in all cases excepting the adipate. In that case, the effectiveness of the mouthpiece as a deaggregator was poor (mean fine particle percent of loaded dose fell from 5.8 to 3.1% showing that the adipate diethanolate was cohesive and difficult to deaggregate).

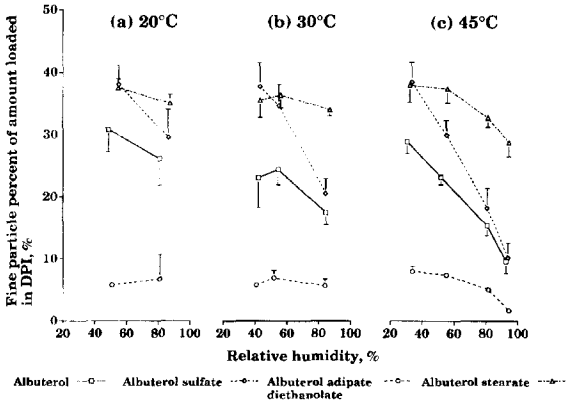


Fig. 7. Fine particle percent of loaded dose versus relative humidity at (a) 20°C, (b) 30°C and (c) 45°C. Error bars are sample standard deviations. Lines are drawn connecting points for the purposes of clarity; data continuity is not implied.

Comparison of fine particle percent between compounds and across conditions depended on whether the loaded or emitted dose was used as a reference. While the emitted dose is most relevant from a clinical and regulatory perspective, presentation of the normalized results for fine particle dose in this paper as 'percent of emitted dose' would be confusing because emitted doses were variable (Fig. 5). Fig. 7 summarizes the results for deposition in stage 2 of the TSI following calculation and presentation as percents of loaded doses, an environment-independent reference condition for all compounds; absolute values for fine particle dose and values relative to emitted doses can be calculated readily from the tabulated results in this paper and Jashnani et al., 1995.

At 20°C and ~ 50% RH, fine particle percents of loaded doses were greatest for the sulfate and stearate salts, followed by albuterol base and albuterol adipate diethanolate. The fine particle percent for all compounds was humidity-dependent at 45°C, although the sulfate and the free base showed most dramatic changes as RH was increased. At 20 and 30°C, however, both the adipate diethanolate and the stearate were largely unaffected by changing humidity while the trend remained with reduced magnitude for the sulfate and base. Overall trends are shown by the coefficients of determination (r^2) obtained from multiple linear regression analyses with humidity and temperature as independent variables (Table 6, row 4). Although performance differences were detected at extremes of temperature and humidity, of greater import are the milder conditions which are more likely to exist during the use of an aerosol formulation. Scheffe's multiple comparison test was used to detect differences in aerosol performance among experiments performed at 20°C (approx. 50 and 80% RH) and 30°C (approx. 40, 50 and 80% RH). No significant differences existed for fine particle percents of emitted

dose or loaded dose of albuterol adipate diethanolate and albuterol stearate while significant differences existed for the fine particle percents of albuterol and albuterol sulfate at the two extremes of environments tested, viz. 20°C, approx. 50% RH and 30°C, approx. 80% RH. While albuterol adipate diethanolate has other undesirable characteristics as evidenced by its highly cohesive nature (low fine particle dose, Fig. 7) and the metastability of the solvate (Table 2), albuterol stearate appeared to provide some useful immunity to temperature and humidity induced changes in fine particle dose. Even though the use of lactose carrier particles in formulated products has been shown to reduce the susceptibility of albuterol sulfate to humidity-induced changes (Hindle et al., 1994), in the case of pure drug metering devices like Turbohaler® (Wetterlin, 1988), it is tempting to hypothesize that stearates and other hydrophobic salts may be more rational salt forms for multi-environment dry powder inhalers.

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