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Dose emissions from marketed dry powder inhalers

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Abstract

The dose emission characteristics of eight marketed dry powder inhalers (DPIs: Intal Spinhaler®, Ventolin and Becotide Diskhalers®, Ventolin and Becotide Rotahalers®, Bricanyl and Pulmicort Turbohalers®, Berotec Inhalator®) have been investigated using the proposed USP dosage unit sampling apparatus for DPIs. Intra- and inter-device variation in emitted doses was determined at air flow rates of 60 and 100 l/min using a 4 l air throughput in each case except Inhalator®, which was tested at 30 l/min only. The sampling apparatus was found to be suitable for quantifying single emitted doses from all of these devices which comprise examples of low, medium and high airflow resistance DPIs (Table 1 footnote). Dose emissions from the DPIs are presented as percentages of the manufacturers' label claims. Under all test flow conditions variability was high, when compared to the uniformity of content standards usually applied to pharmaceutical products; in some cases relative standard deviations (RSD) were greater than 15%, both within and between devices. However, under the proposed USP test flow rate conditions, the total RSD ($n = 25$) was $< 15\%$ around the average emitted dose in all cases except Pulmicort Turbohaler®; such variance (RSD $< 15\%$) is proposed to be acceptable for DPIs delivering current medications. Only the Intal Spinhaler® emitted an average dose similar to its label claim. Testing at 100 l/min vs 60 l/min significantly increased DPI drug emission and reduced the device retention of both the Ventolin® and Becotide® versions of the low resistance devices, Rotahaler® and Diskhaler®. Using these same flow rates for testing the dose emissions from the medium resistance Bricanyl and Pulmicort Turbohalers®, there was no significant difference in drug output between the two flow rates.

Keywords: Dry powder inhaler; Dose emission; Aerosol; Flow rate; Resistance; Pharmacopeial test

1. Introduction

While various dry powder inhalers (DPIs) have been accepted by physicians and patients in Europe and North America (Timsina et al., 1994), pharmacopeias and regulators have yet to define suitable DPI in vitro test methods (Hugossen et al., 1993). Central to any regulatory requirements in the USA will be a need to determine the average drug content in the emitted dose and its uniformity (Byron et al., 1994). Test methods used presently with metered dose inhalers (US

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Pharmacopeia, 1992) are unsuitable for DPIs (Byron et al., 1994); in particular, tests should be performed at a flow rate typical of those to be used by patients inhaling through the device in question (Clark and Hollingworth 1993). Recently, our in vitro sampling apparatus and methodology for DPI dose emission testing (Hindle and Byron, 1993) was adopted as part of a stimulus article by the USP's Advisory Panel on Aerosols (Byron et al., 1994). The primary purpose of this paper is to describe the results of testing a number of commercially obtained DPIs according to the new method; thus adding these results to the public domain. Secondly, we report the dose-modifying effects of varying the air flow rates drawn through these inhalers.

The DPI sampling apparatus (Fig. 1; Hindle and Byron, 1993) used in this paper to determine the emitted dose and its uniformity is described in full detail elsewhere (Byron et al., 1994). The apparatus is essentially an aerosol filter, connected to the DPI mouthpiece, through which a fixed volume of air can be drawn at a known flow rate. The method is flexible with respect to the flow rate to be used during testing; in addition, the volume of air drawn through the inhaler and the duration of the simulated inhalation may be changed. Experimental use of this test apparatus is described with eight marketed DPIs, together with an investigation of the effect of flow on the emitted dose from marketed dry powder inhalers. For each proprietary product, intra and inter-device emitted dose variation is reported.

2. Methods

2.1. Materials

Table 1 lists the proprietary dry powder inhalers (including batch numbers) used in this study. Devices were obtained from commercial sources along with their respective powder preparations for inhalation. With the exception of the Berotec Inhalator® (one device only was available), five devices were obtained and tested. Chemicals and solvents used throughout were HPLC grade and obtained from Fisher Scientific, Raleigh, NC. Water was purified by reverse osmosis.

2.2. Analytical procedures

2.2.1. Albuterol sulfate, terbutaline sulfate and fenoterol hydrobromide

HPLC analysis employed a C-18 Econosphere 5 μm column (25 cm × 4.66 mm, Alltech Associates, Deerfield, IL) with an acetonitrile/water mobile phase (40:60 v/v, albuterol sulfate and terbutaline sulfate; 70:30 v/v, fenoterol hydrobromide), adjusted to pH 3.0 with phosphoric acid and pumped at 1.0 ml/min (Gilson Model

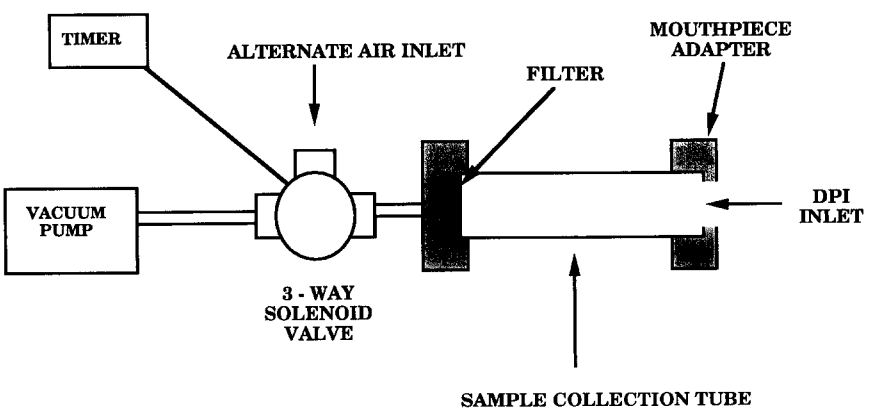

Fig. 1. Dosage unit sampling apparatus (Byron et al., 1994).

302, Middleton, WI). 20 μl samples were injected (Rheodyne model 7125, Cotati, CA) following dissolution and dilution in water (wash solvent). Drug amounts were determined by an external standard peak height comparison to Reference Standard solutions, (albuterol sulfate, Glaxo Inc., Research Triangle Park, NC; terbutaline sulfate and fenoterol hydrobromide, Sigma Chemical Co., St. Louis, MO), accurately prepared and injected in water, following UV detection (Gilson Model 116 Middleton, WI) at 225 nm. All albuterol products containing albuterol sulfate were assayed for albuterol sulfate, the amount of albuterol base being determined by assuming a 2:1 salt stoichiometry, in order for a comparison to be made with albuterol base label claims.

2.2.2. Beclomethasone dipropionate and budesonide

HPLC analysis employed a Partisil 10 μm PAC analytical column (25 cm × 6.4 mm; Whatman, Hillsboro, OR) with a chloroform/methanol/isopropylamine (84.8:15:0.2 by vol.) mobile phase, pumped at 0.5 ml/min (Gilson Model 302, Middleton, WI). 20 μl samples were injected (Rheodyne model 7125, Cotati, CA) following dissolution and dilution in chloroform/methanol (85:15 v/v, wash solvent). Drug amounts were determined by an external standard peak height comparison to Reference Standard solutions, (beclomethasone dipropionate and budesonide, Sigma Chemical Co., St. Louis, MO), accurately prepared and injected in wash solvent, following UV detection (Gilson Model 116, Middleton, WI) at 254 nm.

2.2.3. Cromolyn sodium

Cromolyn sodium was assayed according to the US Pharmacopeia, 1990, using the extinction coefficient (1% w/v, 1 cm) = 164 (British Pharmacopoeia, 1993). Reference standards were obtained from the US Pharmacopeial Convention Inc., Rockville, MD.

2.3. Effect of flow rate on dose emission and DPI device retention

Table 1 employs the data of Clark and Hollingworth (1993) to classify the resistance of each of the dry powder inhalers according to the recent USP Aerosol Panel stimulus article (Byron et al., 1994). According to that article, dose emissions should be determined at 100 l/min (low resistance inhalers), 60 l/min (medium resistance inhalers) and 30 l/min (high resistance inhalers) for 2.4, 4 and 8 s, respectively (4 l air throughput in each case). With the exception of the high resistance Berotec Inhalator®, where the recommended vacuum pump (Byron et al., 1994) was able to draw air at only one of these flow rates (30 l/min), each of the devices was tested at two flow rates, one of which was recommended by the USP stimulus article; the bold text in Tables 1 and 3 shows the proposed USP test conditions (Byron et al., 1994). In order to gain an appreciation of the likely maximum dosing variability (but with the exception of the Berotec Inhalator®, where only one device was available which was tested 10 times), the dose emissions of five devices were determined with five replicate emissions in each case ($n = 25$). The emitted dose uniformity from each inhaler was determined using the 'Dosage unit sampling apparatus for dry powder inhalers' described in detail by Byron et al. (1994) and shown diagrammatically in Fig. 1. All tests were carried out under ambient conditions (21–24°C; 35–60% RH). The sampling apparatus was assembled in a horizontal position with the unloaded DPI in an appropriate mouthpiece adapter to ensure an airtight seal. A 47 mm glass fiber filter type A/E (Gelman Sciences Inc., Ann Arbor, MI) was used in the sampling apparatus. A calibrated flow meter was attached to the total air inlet supply for the DPI. The air flow rate was set (Table 1) by adjusting the vacuum pump, with the alternate air inlet sealed. The timer was then adjusted to enable the pump to withdraw air through the alternate air inlet. Clean DPIs were primed or loaded and subsequently tested according to the manufacturers' labeled instructions. On activation, airflow was diverted, via the three-way solenoid valve, through the DPI for the appropriate interval (Table 1), after which flow was diverted back through the alternate air inlet. The contents of a single emitted dose from the DPI were discharged into the collection tube. The DPI was detached from the sampling appa-

Table 1
Summary of dry powder inhalers tested in this study alongside the test flow conditions applied in each case

Proprietary names and dose label claim	Active ingredient	Batch numbers (number of devices and/or packaged powders for inhalation)	Resistance [a]	Test flow conditions [a]
Intal Spinhaler (supplied as)	cromolyn		low	60 l/min for 4 s
Spinhaler	sodium	ATK11B (×5)		**100 l/min for 2.4 s**
Intal capsules 20 mg		JE4501B1 (×4)		
(Fisons, UK)		JE38C (×1)		
Ventolin Diskhaler (supplied as)	albuterol		low	60 l/min for 4 s
Ventodisks 400 μg	sulfate	W7672MC (×5)		**100 l/min for 2.4 s**
(Allen and Hanburys, UK)				
Becotide Diskhaler (supplied as)	beclomethasone		low	60 l/min for 4 s
Becodisks 400 μg	dipropionate			**100 l/min for 2.4 s**
(Allen and Hanburys, UK)		W9622LA (×5)		
Ventolin Rotahaler (supplied as)	albuterol		low	60 l/min for 4 s
Rotahaler	sulfate	S39999M (×5)		**100 l/min for 2.4 s**
Ventolin Rotacaps 400 μg		S1602NC (×5)		
(Allen and Hanburys, UK)				
Becotide Rotahaler (supplied as)	beclomethasone		low	60 l/min for 4 s
Rotahaler	dipropionate	S41080N (×5)		**100 l/min for 2.4 s**
Becotide Rotacaps 400 μg		S1773AB (×2)		
(Allen and Hanburys, UK)		S1602LA (×3)		
Bricanyl Turbohaler (supplied as)	terbutaline		medium	**60 l/min for 4 s**
Bricanyl Turbohaler 500 μg	sulfate	SH53 (×5)		100 l/min for 2.4 s
(Astra Draco, Sweden)				
Pulmicort Turbohaler (supplied as)	budesonide		medium	**60 l/min for 4 s**
Pulmicort Turbohaler 400 μg		SH221 (×5)		100 l/min for 2.4 s
(Astra Draco, Sweden)				
Berotec Inhalator (supplied as)	fenoterol		high	**30 l/min for 8 s**
Berotec 200	hydrobromide			
(Boehringer Ingelheim, Germany)		22982 (×1)		

Flow conditions shown in bold are the proposed USP test flow rates (Byron et al., 1994). [a] USP proposed protocol for DPIs (Byron et al., 1994). Low resistance: $R \leq 0.07\ (\mathrm{cmH_2O})^{1/2}\ \mathrm{l}^{-1}$ min test at 100 l/min for 2.4 s. Medium resistance: $R \geq 0.07\ (\mathrm{cmH_2O})^{1/2}\ \mathrm{l}^{-1}$ min and $R \leq 0.12\ (\mathrm{cmH_2O})^{1/2}\ \mathrm{l}^{-1}$ min test at 60 l/min for 4 s. High resistance: $R \geq 0.12\ (\mathrm{cmH_2O})^{1/2}\ \mathrm{l}^{-1}$ min test at 30 l/min for 8 s. A total of 4 ± 0.2 l of air was drawn through each inhaler in all cases.

Table 2
Reproducibility and accuracy data for the chromatographic assays used in this study

Drug	Retention time (min)	Reference Standard RSD ($n = 10$) (%) (precision) [a]	Nominal concentration of standard solution (mg/l)	Mean (RSD) measured concentration standard solution (mg/l) (accuracy) [b]
Albuterol sulfate	5.5	1.38	10	10.16 (1.09%)
Terbutaline sulfate	5.5	1.27	10	9.90 (1.43%)
Fenoterol hydrobromide	8.0	2.29	8	8.09 (1.70%)
Beclomethasone dipropionate	4.6	2.01	16	15.55 (1.96%)
Budesonide	4.6	1.61	16	15.84 (1.49%)

[a] Precision was assessed by the relative standard deviation of the peak height from 10 replicate injections of Reference Standard solution.
[b] Accuracy was assessed by the calculating the measured concentration of a standard solution using peak height comparison to the Reference Standard solution ($n = 5$).

ratus. Using the wash solvents described above for reference standard preparation, drug was washed and collected from the sampling apparatus. In the case of the Diskhaler® and Rotahaler®, the device and unit dose container (Rotacap® capsule or Diskhaler® blister) were also washed to determine the amount of drug retained by the inhaler. Drug amounts in these test solutions were quantified using the previously described assay procedures.

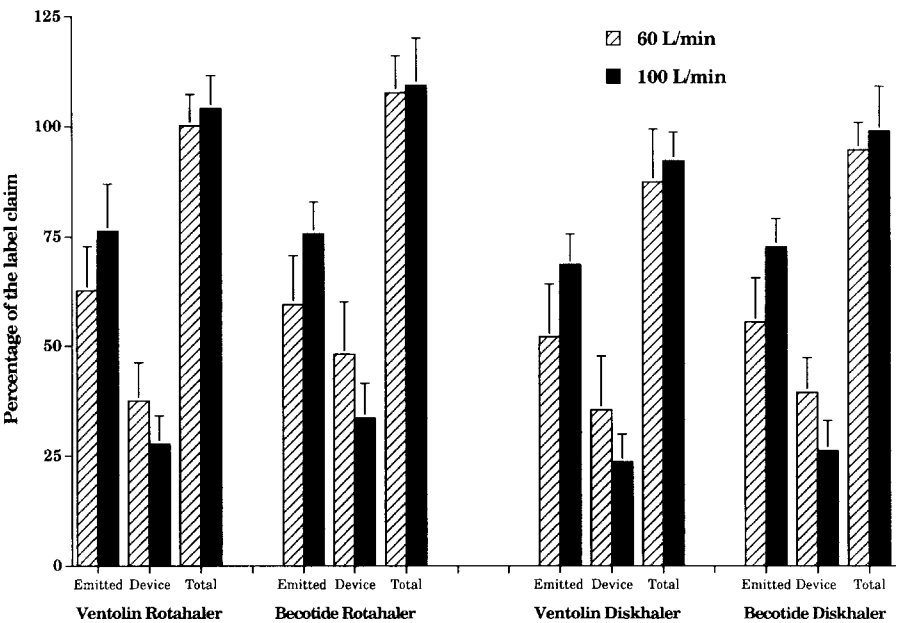

Fig. 2. Summary of mean (SD error bars) inter-device dosage emissions and device retention at 60 and 100 l/min for the Rotahaler® and Diskhaler® (five devices, five replicates, total $n = 25$). Mass balance was demonstrated in each case where mean (SD) total drug recovery when tested at 60 l/min was 100.2 (7.1)%, 107.6 (8.4)%, 87.4 (11.9)% and 94.7 (6.2)% of label claim, in the case of Ventolin Rotahaler®, Becotide Rotahaler®, Ventolin Diskhaler®, Becotide Diskhaler®, respectively. Similarly, when tested at 100 l/min, 104.1 (7.5)%, 109.3 (10.7)%, 92.2 (6.5)% and 98.9 (10.1)% of label claim, for the Ventolin Rotahaler®, Becotide Rotahaler®, Ventolin Diskhaler®, Becotide Diskhaler®, respectively. A constant volume of 4 l of air was drawn through each device at each flow rate.

2.4. Statistics

Dose emissions were compared between the two flow conditions using an unpaired t-test for data with assumed equal variances.

3. Results and discussion

3.1. Analytical procedures

Table 2 shows reproducibility and accuracy of the chromatographic assays used in this study. Drug concentrations used were similar to those expected from test solutions. Reproducibility was shown as the relative standard deviation (RSD) of the peak height calculated from ten replicate injections of a Reference Standard solution. The accuracy of the external standard method was assessed by injection of a standard solution of nominal concentration (Table 2), then using peak height comparison to the Reference Standard solution to calculate the concentration of the nominal standard. Five replicates were performed, the mean concentration of the standard solution and its relative standard deviation are shown in Table 2.

3.2. Method validation

The sampling apparatus was found to be suitable for quantifying single emitted doses from all dry powder inhalers tested in this study. The aerosol retention characteristics and the drug binding (from wash solvent) properties of the glass fiber filter (Fig. 1; Byron et al., 1994) were tested for each proprietary inhaler and drug respectively, prior to performing dose emission tests. To validate the aerosol retention characteristics of a single filter, a dose emission test was performed with each inhaler in turn, with a second glass fiber filter placed in series with the first. No active ingredient penetrated the first filter as a dry powder aerosol in any of these experiments. Subsequent experiments were performed with a single glass fiber filter. In blank experiments, drug solutions of known concentrations in wash solvents were introduced to the sample collection tube (Fig. 1), active ingredients failed to selectively adsorb to any part of the test apparatus.

Table 3
The accuracy and reproducibility of dose emissions from dry powder inhalers, expressed as a percentage of the label claim

DPI	Flow rate (l/min)	Device 1	Device 2	Device 3	Device 4	Device 5	Total
Intal	60	101.3 (10.6)%	100.3 (7.5)%	100.2 (9.3)%	101.8 (7.7)%	97.5 (3.5)%	100.2 (7.6)%
Spinhaler	**100**	**89.6 (7.4)%**	**89.9 (4.2)%**	**86.8 (15.0)%**	**85.3 (11.7)%**	**90.5 (5.4)%**	**88.4 (8.9)%**
Bricanyl	**60**	**56.1 (9.8)%**	**60.3 (17.6)%**	**65.4 (17.9)%**	**66.4 (11.4)%**	**64.3 (5.1)%**	**62.5 (13.7)%**
Turbohaler	100	68.9 (24.4)%	71.9 (22.8)%	72.1 (14.4)%	66.0 (34.4)%	66.4 (11.4)%	69.1 (21.1)%
Pulmicort	**60**	**48.0 (25.0)%**	**69.6 (7.0)%**	**62.4 (13.8)%**	**54.3 (13.3)%**	**56.3 (12.1)%**	**58.1 (18.3)%**
Turbohaler	100	63.3 (26.4)%	50.3 (19.1)%	72.4 (37.8)%	72.1 (26.9)%	70.2 (24.2)%	65.7 (29.3)%
Ventolin	60	67.3 (7.1)%	55.7 (24.6)%	60.6 (19.3)%	68.7 (7.7)%	61.1 (16.0)%	62.7 (16.1)%
Rotahaler	**100**	**75.8 (19.8)%**	**76.2 (18.0)%**	**71.1 (8.3)%**	**75.7 (9.6)%**	**82.9 (11.6)%**	**76.3 (14.0)%**
Becotide	60	59.7 (19.4)%	50.1 (28.1)%	62.3 (9.6)%	66.9 (17.3)%	58.6 (12.8)%	59.5 (18.8)%
Rotahaler	**100**	**73.2 (7.1)%**	**78.5 (10.9)%**	**72.0 (12.1)%**	**75.3 (6.6)%**	**79.6 (9.4)%**	**75.7 (9.5)%**
Ventolin	60	39.5 (20.2)%	55.1 (20.1)%	45.8 (17.5)%	63.8 (17.0)%	56.3 (13.3)%	52.0 (23.3)%
Diskhaler	**100**	**66.6 (9.5)%**	**70.8 (12.0)%**	**67.6 (11.2)%**	**65.5 (8.5)%**	**72.6 (10.1)%**	**68.6 (10.2)%**
Becotide	60	68.0 (4.8)%	52.9 (18.1)%	53.4 (17.4)%	46.9 (20.5)%	55.8 (10.6)%	55.4 (18.3)%
Diskhaler	**100**	**67.2 (1.9)%**	**73.6 (3.9)%**	**79.9 (7.9)%**	**75.2 (8.5)%**	**67.7 (6.1)%**	**72.7 (8.8)%**

Within-device dose emission variability is shown as the mean (relative standard deviation) for five doses from five devices. In addition, between-device variation is shown as the total mean (RSD) dose emission from all five devices ($n = 25$). Results shown in bold are the proposed USP DPI test flow rates (Byron et al., 1994). The mean (RSD) dose emitted from a single Berotec Inhalator was 71.6 (9.3)%, expressed as a percentage of label claim, when tested at 30 l/min for 8 s ($n = 10$).

Fig. 2 and its legend shows that good mass balance was observed at both flow conditions compared to the label claim, when total drug recovery was calculated for Ventolin® and Becotide® delivered via both the Rotahaler® and Diskhaler® DPI delivery systems.

3.3. Dose emissions

Table 3 shows the measured accuracy and reproducibility of dose emissions (dosage uniformity) from each of the eight products. For comparative purposes, the emitted percent (Table 3 and Fig. 2) was calculated as the amount of drug leaving the inhaler expressed as a percentage of the product label claim. Device retention was expressed similarly (Fig. 2).

Because there was no standard method applied by each manufacturer to arrive at label claim, the results cannot be simply compared as if the percents emitted (Table 3) are also device emptying efficiencies. The Intal Spinhaler® (UK formulation) for example, uses capsules in which some 10% overage is incorporated (British Pharmacopoeia, 1993). Overage may or may not be included in capsules for the Rotahalers® and Inhalator® and/or dosing wells in each of the disks for the Diskhalers® (although the data in Fig. 2 imply that the Glaxo products contain no overage). Label claim in the case of each of the Turbohalers® (Table 1) cannot be determined independently because proprietary techniques are used to assess the dose metered from the drug reservoir.

Table 3 presents data for average percent of label claim emitted from each inhaler at different flows. The table can be used to determine inter- and intra-device variation in aerosol drug emission. Numbers in parentheses are relative standard deviations (RSD, $n = 5$) in each case. The flow scenario in bold print for each inhaler is that recommended by the USP Aerosol Panel for testing (Byron et al., 1994). In the final column of the table, the average emission across all devices and the relative standard deviation for this worst case test scenario (combined variance of five different devices) are presented ($n = 25$). The variability of dose emissions from DPIs was found to be relatively high, often with RSD > 15%, both within and between devices. At the recommended flow rates, however (Table 3, bold type; Byron et al., 1994), total RSD was less than 15% about the average emitted dose in all cases except Pulmicort Turbohaler®. With this exception, this result shows that emitted dose variations for these DPIs fell within the RSD ≤ 15% criterion presently established for pressurized MDIs (US Pharmacopeia, 1992; Byron, 1994) and advocated for use with DPIs by the USP Aerosol Panel (Byron et al., 1994) for drugs currently administered via inhalation for the treatment of lung disorders. The larger RSD associated with Pulmicort Turbohaler® currently represents an interesting regulatory dilemma within the USA. The Turbohaler® device is probably one of the best accepted by patients in Europe and many papers attest to its efficacy, safety and acceptability (Osterman et al., 1991; Andersson et al., 1993). Some of the dosing variations associated with Turbohaler® are manifestations of Astra Draco's unique and laudable attempts to meter very small doses of pure drug from a reservoir contained within the device itself (other devices use cumbersome external metering techniques and/or powder diluents). The European Pharmacopeia and product regulators have recognized this fact in their recommendations for dosing uniformity for DPIs (Inhalanda, 1993). The regulatory hurdle in the USA can be captured by two questions relating to dosing specifications which have implications for clinical testing: 'Should a larger than usual dosing variance be used to exclude (from the US market) some drug forms presented in one of the most clinically acceptable inhalers?' and, if not, 'Should wide dosing variance be applied for all DPIs?' Given the enormous dosing variability associated with deposited doses of drug in the diseased lungs of patients from inhalation devices (Newman et al., 1981), and the possibility that this variance may swamp the dosing variability in the case of Turbohaler® delivered drugs, the design of clinical testing protocols may or may not need to be modified to provide the regulators with adequate proof of safety and efficacy.

Only the Intal Spinhaler® emitted an average

dose similar to its label claim. The emitted doses from all other devices were significantly lower, reflecting non-ideal emptying and the fact that label claims reflect metered, rather than emitted, doses. Although unit dose packaging also requires a label claim, the absence of emitted dose labeling is contrary to the USP Aerosol Panel's recent recommendations (Byron et al., 1994).

3.4. Effect of flow rate on dose emission testing

Testing at 100 l/min compared to 60 l/min, significantly ($P < 0.05$) altered the dose emission and device retention characteristics of the Rotahaler® and Diskhaler®, for both the Ventolin® and Becotide® products (Fig. 2). Dose emission was increased at the higher flow rate, while between- and within-device variation was reduced. The other low resistance device, the Intal Spinhaler®, showed a different trend. Dose emission was seen to decrease significantly at the higher flow rate. No significant dose emission differences were observed with the medium resistance Turbohaler® when tested at 60 and 100 l/min, with both Bricanyl® and Pulmicort® ($P > 0.05$) no doubt because of the large variance in dose emissions within and between devices at both flow rates. Similar patterns of device retention and dose emission were observed for the Diskhaler®, Rotahaler® and Turbohaler®, at both flow rates, irrespective of the drug being tested. The Berotec Inhalator® was only tested at 30 l/min (higher flows were impossible with the recommended vacuum pump) in accord with the USP Aerosol Panel's recommendation (Byron et al., 1994) and reflecting a probable flow rate achieved in practice (Clark and Hollingworth 1993). The mean (RSD) dose emitted from a single Berotec Inhalator® was 71.6 (9.3) %, expressed as a percentage of label claim ($n = 10$).

4. Conclusions

The dosage unit sampling apparatus provides an adaptable and suitable method of assessing the dose emissions from a variety of low, medium and high resistance dry powder inhalers at multiple air flow rates. The aerosol capture efficiency of the dosage unit sampling apparatus was demonstrated in each case. Mass balance from total drug capture studies with the Diskhaler® and Rotahaler® was documented. The dose emitted from the DPIs was shown to be variable, with respect to both within-device and between-device dose emissions. However, this variability was reduced when the DPIs were tested using the USP recommended air flow rate conditions. The choice of suitable test flow conditions was found to be a critical variable determining the emitted dose from dry powder inhalers. Future compendial tests for dry powder inhalers should employ flow rates related to the airflow resistance of the DPI.

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