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Metered-dose inhalers I: drug content and particle size distribution of beclomethasone dipropionate

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Abstract

Four commercially available beclomethasone metered dose inhalers were analyzed for both spray content uniformity and particle size. The drug contents of primed and unprimed sprays collected at the beginning of the lifetime of the canister were not significantly different from those collected throughout the experiment. Particle size analysis of the four products using the Andersen Cascade Impactor Mark II showed that the distribution profiles were not identical.

An existing HPLC method was modified to quantitate single sprays for content uniformity and to measure the amount on an impactor stage for particle sizing.

Keywords: Anderson cascade impactor; Beclomethasone dipropionate; Content uniformity; Metered-dose inhalers; Particle size distribution

1. Introduction

The variability of the delivered dose in individual sprays from some metered-dose inhaler (MDI) products has been demonstrated in past reports [1–5]. Drugs studied included salbutamol, fenoterol, and cromolyn sodium. Previous work of the authors related to MDIs led to the proposal [1] of a sampling scheme for the rigorous evaluation of MDI products for single spray content uniformity. The scheme included studying products stored in both the valve-up and valve-down positions and after rest periods equivalent to the dosing interval of the drug.

Particle size analysis of inhaled drug products is also an important factor in characterizing their performance. The Anderson Cascade Impactor has become one of the foremost tools for performing analysis. This device is currently one of three described in the United States Pharmaco-

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poeia (USP) [6] for the characterization of MDIs. However, the USP Advisory Panel on Aerosels recently recommended [7] that this device, or an equivalent, should be definitive for the testing of MDIs. It is also one of four acceptable devices recognized by the European Pharmacopoeia (EP) [8]. Previous work of the authors has involved the exclusive use of this device for the determination of the particle size distribution of products from selected manufacturers of salbutamol [9].

Beclomethasone dipropionate (BDP), a corticosteroid with strong topical and weak systematic effects is sold in several forms for inhalation. The MDI unit contains a microcrystalline suspension of BDP–trichloromonofluoromethane clathrate in a mixture of propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid [10]. A dose of one or two sprays every 6 h and a maximum daily dose of 1000 μg is indicated on the package insert.

The study reports the results of the unit spray content uniformity determination and the particle size analysis of products currently on the Canadian market. A modification of the previously described sampling was used. Samples were taken only over the initial spray interval and only the valve-down position and 6 and 16 h rest periods were used [1].

Particle size measurement using the Anderson Cascade Impactor Mark II is based on the device's ability to trap particles according to their increasing aerodynamic diameter. There are eight stages or effective cutoff diameters (ECDs) at irregular intervals. A graph of weight of drug on each stage versus the stage's ECD is termed a particle size distribution profile. This distribution of the drug for a spray or a group of sprays has traditionally been assumed to be log-normal. To characterise the drug in a spray, summary parameters such as the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) are estimated. The MMAD is the aerodynamic diameter that, on a mass basis, one-half of the measured particles are less and than one-half are greater than. The GSD is a measure of the spread of particles around this median.

The fine particle dose or fraction [6,11] is the portion of inhaler output having diameters considered suitable for deposition and retention in the respiratory tract. Generally, this fine particle fraction is considered to be in the 1–7 μm range [11] but its definition depends on the ECD ranges of the device and the target area in the lungs for the drug substance. An estimate of the drug dispersed can be made by calculating the total mass of particles within particle size ranges specific for the drug substance. The total on the stages containing the MMAD plus two stages on either side can be used for one such estimate. This parameter is referred to below as the MMAD $\pm$ 2 stages. The calculation of all of these parameters assumes that the distribution is log-normal, the errors at each point on the curve are equal and the particles are spherical.

Many of these mathematical manipulations and assumptions may be eliminated by characterizing a particle size distribution using other parameters, for example a W_{max} (the maximum mass) and an ECD_{max} (the effective cut-off diameter of the stage where W_{max} resides). For summarizing a given product an overall ECD_{max} for all sprays is required from which $\pm$ 1 or $\pm$ 2 stages could define the fine particle fraction. The ECD_{max} used in the parameters $ECD_{max} \pm 1$ or ± 2 stages is the most frequently observed (mode) for that product. Another measure of the fine particle fraction would be the total mass of particles over a series of stages. Fr_{15} (the mass of all particles found on stages between 1.1 and 4.7 μm, stages 3–5) has been chosen as an example for this study. All of these parameters may be calculated from the analytical results with minimal mathematical manipulation.

The products in this study were therefore evaluated based on the following parameters: MMAD, GSD, MMAD $\pm$ 2 stages, W_{max}, $ECD_{max} \pm 1$ and ± 2 stages, and Fr_{15}.

The USP method of assay is based on HPLC quantitation and therefore was evaluated for the determination of BDP drug content for this study and was found to have limitations with respect to analytical efficiency. Of other reported HPLC methods for the determination of BDP in drug substance raw materials [12,13] the method of Mulholland and Rudd [12] was chosen for modifi-

Table 1
Single spray BDP content for two canisters of four products (% label claim)

Spray no.	Spray type	E1[a]	F1[b]	G1[a]	H1[a]
1	P[c]	105, 107	117, **131**	109, 90	89, 99
2	P	103, 119	103, 100	94, 95	96, 102
3	P	99, 112	98, 99	94, 113	105, 94
4	P	80, 98	100, 98	92, 87	108, 97
6	P	81, 90	102, 104	93, 85	87, 87
8	P	77, 91	101, 98	87, 80	97, 104
10	P	108, 95	115, 103	90, 80	110, 97
12	P	103, 110	116, 116	92, 82	94, 115
7	UPT[d]	**73**, 94	99, 112	97, **73**	78, 84
11	UPT	92, 92	103, 111	108, 91	92, 92
5	UPO[e]	**72**, 89	81, 100	103, 77	85, 96
9	UPO	81, 95	104, 95	92, 93	86, 97
Means:	P	99 (12)	106 (9)	91 (10)	99 (8)
	UPO	84 (12)	95 (11)	92 (12)	91 (7)
	UPT	88 (11)	106 (6)	92 (16)	87 (8)

[a] Label claim of 50 μg per spray.
[b] Label claim of 250 μg per spray.
[c] Indicates a primed spray.
[d] Unprimed spray, $T = 6$ (UPT).
[e] Unprimed spray, $T > 16$ h (overnight) (UPO).

cation because it was capable of resolving beclomethasone dipropionate from its related compounds, it was an isocratic system and it gave a short retention time for the drug.

2. Experimental

2.1. Experimental design

Two canisters of each available lot were tested for spray content uniformity. The collection scheme, the sampling sequence and the results are shown in Table 1. Two canisters from a single lot for each of the four available products were sampled for particle sizing over 4 days in a duplicate 4 × 4 latin square design. A second lot was not available from manufacturer G hence the sample scheme to collect the second lot was modified to examine two cans per lot over 2 days for three manufacturers.

2.2. Sample collection

Single sprays from BDP MDIs were collected using the USP Unit Spray Sampling Apparatus [6]. Air was drawn through at a rate of 12 ± 1 l min^{-1}. A stopwatch was used to time all intervals to ensure uniformity throughout the experiment.

Sample sprays were collected by the following method for primed and unprimed sprays. The vacuum pump was turned on, the air flow calibrated, the sample shaken for 5 s and the MDI inserted into the collection apparatus. The valve on the MDI was than depressed for 1 s, expelling the spray. The pump was turned off after 5 s. The apparatus and the actuator were rinsed and quantitatively collected for analysis, in 100 ml and 50 ml volumetric flasks respectively. The actuator was dried using a short burst of compressed air. Before spray 1, all canisters had a spray fired to waste to lubricate the valve, then the actuator was thoroughly rinsed and the canisters remained valve-down throughout the entire experiment.

Unprimed sprays were collected after allowing the canister to rest for 6 h overnight prior to sampling. The sample was shaken for 5 s, valve-down, and then discharged into the collection apparatus as described above.

Using an Anderson Cascade Impactor Mark II, two primed sprays from BDP MDIs were collected

to characterize particle size. Air was drawn through the apparatus by a vacuum pump (Doerr Electric Model 0322-V4B-GI8DX) at a rate of 28.3 l min^{-1} as measured with a Galibrator system (Gilian Instrument Model D-800270). A stopwatch was used to time all intervals to ensure uniformity throughout the experiment.

Each canister was primed with three sprays before use. Sample sprays were collected as per the following method: the vacuum pump was turned on, the air flow set to 28.3 l min^{-1}, the sample was shaken for 5 s and the MDI inserted in the mouthpiece adaptor on the induction port. The valve on the MDI was then depressed for 1 s, expelling the spray; the pump was turned off after 5 s. 30 s were than allowed to elapse before the second spray was collected in the same manner. Each stage of the apparatus and the corresponding collection plate was rinsed and collected in a 25 ml volumetric flask for quantitative analysis. The actuator was rinsed and then dried using compressed air.

2.3. HPLC conditions

The HPLC system consisted of a pump (Varian 2010 HPLC Pump), a variable wavelength detector set at 240 nm (Varian Star 9050 Variable Wavelength UV–VIS Detector), an autosampler with a 20 μl loop (Waters WISP 710B Autosampler), an integrator with a disk drive (Hewlett-Packard HP3396A and 9122C respectively), and a CSC-Exsil Octyl-B 100×4.6 mm^2, 3 μm column (# 069217). The system was operated at ambient temperature with a mobile phase flow rate of 1 ml min^{-1}. Mobile phase was acetonitrile–water (50:50, v/v) passed through a 0.45 μm filter.

2.4. Solutions

Methanol was used for all solutions. Resolution solution; 1 μg ml^{-1} each of BDP and budesonide. Standard solution: a seven point calibration curve consisting of solutions with concentrations ranging from 0.01–10 μg ml^{-1} BDP for content uniformity and a five point calibration curve ranging in concentration from 0.025–1 μg ml^{-1} for particle size measurement.

2.5. System suitability

Assay six samples of resolution solution, the relative standard deviation is less than 3%. The efficiency, calculated on the BDP peak, is greater than 20 000 theoretical plates ml^{-1} for BDP. The resolution is at least two and the tailing factor less than 1.5.

2.6. Procedure

Inject separately 20 μl of each of the solutions in the calibration curve and the test solution into the chromatograph and run for 6 min. Calculate the amount of BDP in micrograms in the test solution using a weighted linear regression.

2.7. Calculation of MMAD and GSD

The particle size distribution for any given spray was assumed to be log-normal. After taking the natural logarithms of the ECDs two different methods were used to estimate the mean and standard deviation of the resulting normal distribution. The MMAD and GSD are then found by taking the antilog of the mean and standard deviation respectively. Method one (subscripted USP) is based on the USP [6] algorithm which estimates a weighted linear regression for the probit line formed from the percent plate cumulative amount over the amount in the device. Since summing random variables increases variance, a weight factor equal to the number of plates summed was used. A second method developed in this lab (subscripted SAS) implements PROC LIFEREG™ of SAS® [14] and is based on the censored maximum likelihood algorithm which estimates the normal parameters using the raw data from each plate, thus there is no summing of amounts. Since each plate has a range of particle sizes, the censoring feature of LIFEREG™ is important.

3. Results and discussion

For the initial sprays (1–4), all of which were primed, only one product, F1, had a single value (131%) above 125% (mean 124%) of the label

claim. However, after this spray, the average drug content of all products fell between 80 and 120% of the label claim. Variation about the mean for primed sprays was less than 15% for all products. A summary of the values generated, per product, is given in Table 1.

Unprimed sprays were collected after a rest period of 6 h (dosing schedule suggested in the package insert) or > 16 h [1]; the canisters were stored in the valve-down position. Three of the values were below 75%. These were: one spray from E1 after an overnight rest, UPO; and one each from E1 and G1 after a 6 h rest, UPT. The average drug content ranged between 84 and 106% of the label claim. The average variability in the unprimed sprays was similar to that exhibited by the above-mentioned prime sprays.

The average amount of drug retained on the actuator (% label claim) for products E1, F1, G1 and H1 were 7 μg (14%), 33 μg (13%, 250 μg product), 11 μg (22%), and 8 μg (17%) respectively. These averages do not include spray number one. The first measured primed spray was not included in these calculations as previous studies had shown that the first spray often constituted a significantly larger dosage. In this study only sample F1 exhibited this phenomenon. It is to be noted that the amounts reported in Table 1 include the amount on the actuator.

Currently the USP content uniformity [15] requirement for MDIs specifies the initial determination of the contents of 10 dosage units of a product. Products are acceptable if not more than one of the dosage units is outside 75–125% and none are outside 65–135%. If two or three dosage units are outside 75–125%, an additional 20 dosage units must be sampled. Products are acceptable if no more than three units are outside 75–125% and none are outside 65–135%. These limits are similar to those of the EP [8] where the assay average is used as the fiducial reference for the imposition of 75–125% limits. Neither publication specifies which 10 sprays are to be analyzed. The USP Advisory Panel on Aerosols [7] recently reaffirmed these limits but solicited data from interested parties to evaluate these and a stricter (80–120% and 75–125%) set of limits that had been proposed by the Food and Drug Administration. Results submitted [5] by the Pharmaceutical Research and Manufacturer's Association (PhRMA) on the testing of 21 products by 10 companies indicated that the stricter limits would lead to a significant increase in nonconforming lots.

The products tested in this study were sampled using a scheme involving 12 sprays which included both primed sprays and those after two rest periods. The results indicated that H1 passed unequivocally. Products F1 and G1 also passed based on the first 12 sprays; F1 had one value, spray number 1, above 125% but below 135% and G1 had one value, after a 6 h rest, below 75% but above 65%. Product E1 would have required 20 subsequent samples to determine its status as two values from the first 10 from one canister were below 75% but above 65%; these sprays were analyzed after rest periods of 6 and 16 h. These low results for unprimed sprays are consistent with previous results from this laboratory [1] and indicate that the incorporation of rest periods into the sampling scheme would provide a more discriminating evaluation of products.

Fig. 1 presents a graph of the mean weight ($n = 8$) and range of weights per stage against

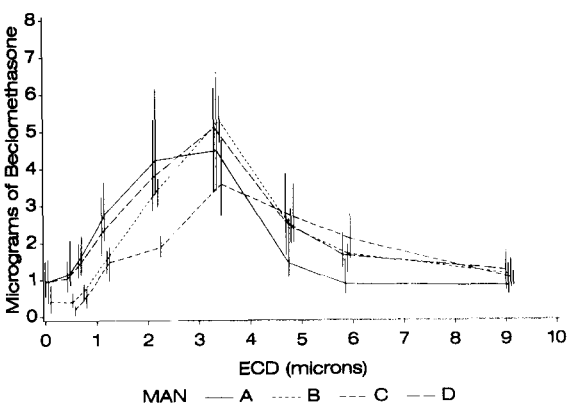

Fig. 1. Particle distribution profile for all manufacturer's products- E1(A), F1(B), G1(C) and H1(D); ($n = 8$; the range of amounts on each stage is indicated by the vertical bars).

Table 2
Manufacturer comparison of curve parameters ($n = 8$)

Manufacturer	E1	F1	G1[a]	H1
MMAD[bd] ± 2 stages (RSD) (μg)	14.6 (22)	13.5 (5)	10.2 (15)	15.1 (19)
ECD_{max} (RSD) (μm)	3.1 (11)	3.3 (0)	3.3 (0)	3.3 (0)
ECD^{b}_{max} ± 1 stage (RSD) (μg)	10.2 (24)	11.2 (8)	8.2 (22)	11.4 (21)
ECD^{b}_{max} ± 2 stage (RSD) (μg)	13.8 (23)	14.5 (6)	11.8 (18)	15.4 (20)
Wmax (RSD) (μg)	4.6 (24)	5.3 (9)	3.6 (25)	5.1 (19)
Fr15 (RSD) (μg)	11.5 (21)	10.3 (5)	7.0 (13)	11.2 (19)
$MMAD_{SAS}$[c] (RSD) (μm)	2.34 (7)	3.30 (7)	3.85 (11)	2.81 (10)
GSD_{SAS}[c] (RSD) (μm)	2.32 (7)	2.04 (9)	1.84 (10)	2.30 (11)
$MMAD_{USP}$[d,e] (RSD) (μm)	2.28 (7)	3.61 (9)	4.13 (12)	2.93 (10)
GSD_{USP}[de] (RSD) (μm)	2.63 (9)	2.79 (11)	2.19 (14)	2.88 (11)

[a] Based on $n = 4$ observations.
[b] Based on the measured $MMAD_{SAS}$ of a reference product (E1).
[c] Calculated using LIFEREG SAS®.
[d] Calculated using USP ⟨601⟩ procedure.
[e] A weighted least-squares regression was used ($1/n$; n = no. of observations) to achieve the best fit.

ECD of each stage of the Andersen Impactor, termed a "particle distribution profile". These particle size distribution profiles show the variation in the particle sizes among the four products tested.

The curves generated by F1 and H1 are visually most similar; these products show a greater preponderance of particles on the 3.3 μm stage. Both E1 and G1 have flattened curves compared with the sharp curves generated by the other two products. Product E1 has a larger portion of particles in the 2.1 μm range; G1 has a larger portion of particles in the 4.7 and 5.8 μm ranges.

Table 2 contains curve parameters and RSD about the mean for the products examined. It should be noted that where microgram values appear in the Table for product F1 (250 μg dosage) they have been normalized to the 50 μg dosage level. The MMAD values, calculated using both SAS® and USP method, are similar and display the same trends. Both sets of values are included in Table 2 and both indicate significant differences for product G1 which had proportionally fewer small particles than the other three. The $MMAD_{SAS}$ for the four products ranged from 2.34 (E1) to 3.85 (G1), a variation of 21%. The RSD of the $MMAD_{SAS}$ of the four products ranged from 7–11%. It is interesting to note that in spite of the visual similarity of the F1 and H1 profiles, there are substantial differences between both MMADs [(3.30 and 2.81 μm)$_{SAS}$ and (3.61 and 2.93 μm)$_{USP}$] for these products. These products can be distinguished by their MMADs. The MMADs of the other two products, E1 and G1, differ greatly, as would be expected from the curves. It is interesting that for products E1 and F1, which are manufactured by the same company, significant differences can be detected in the particle size distributions. The distribution curve of product F1, which delivers five times the dose of E1, indicates that the product has significantly more larger particles than product E1. The MMAD values for the two products are consistent with this observation. This may be due to an increased number of particles in the droplets of product F1, resulting in less primary particles and more aggregates of higher aerodynamic diameters [16,17].

The GSD_{SAS} ranged from a minimum of 1.84 (G1) to a maximum of 2.32 (E1) and the GSD_{USP} ranged from 2.19 (G1) to 2.88 (H1).

It is important to note the effect of the differences in the calculated $MMAD_{SAS}$ and $MMAD_{USP}$ for product F1 in regard to estimating the fine particle fraction using MMAD plus the 2 stages on either side. The ECD of the nearest stage of the Anderson Impactor is 3.3 μm. This difference means calculations of MMAD ± 2

stages using these two MMADs would result in the definition of different particle size fractions. This highlights the need for the consistent specification of calculation methods. Future discussion of MMAD ± 2 stages refers to the fraction specified by $MMAD_{SAS}$. The MMAD ± 2 stages can be calculated in two ways. The first would be to use the MMAD experimentally determined for each product; the second would be to use the MMAD as determined for a reference product. For these products we have arbitrarily chosen product E1 as the reference product. Both values are given in Table 2. It is evident that if the range of particles is allowed to vary with the experimentally determined MMAD of the product the ranges of particles may differ from one product to another. This is demonstrated in the case of product G1. Using the reference product's MMAD, the MMAD ± 2 stages includes particles on the five Andersen stages having cut-off diameters between 0.65 μm and 4.7 μm. Using the MMAD experimentally determined for G1, the MMAD ± 2 stages includes particles on the five stages having diameters between 1.1 μm and 5.8 μm. The numeric difference is small, 10.2 vs. 11.8 μg, but the dissimilarity in the definition of the fractions may mask significant differences in the performance of the product. Therefore it would seem prudent to specify consistently the MMAD ± 2 stages. However, it must be recognized that the MMAD ± 2 stages is model-dependent and cannot be used for a drug whose MMAD lies on one of the extreme stages of the impactor device.

W_{max}, the maximum weight observed on a stage, also demonstrated significant differences among products. However, this parameter does not entirely reflect the particle size distribution of products. This is particularly true in the case of product E1 where a more even distribution of particles occurs over two stages, resulting in a lower W_{max}.

The values of ECD_{max} are the result of an average of all determinations. Where the ECD_{max} is consistent for all measurements it falls on a cut-off diameter of the device and the RSD is zero. In the case of product E1, one of the measurements resulted in the largest portion of particles on the stage with an ECD of 2.1 μm. Variation in this value for a product only then indicates a more nearly equal distribution of particles over two or more stages. It does not by itself describe the particle size distribution of products.

The $ECD_{max} \pm 1$ or 2 stages is similarily able to detect differences among products; in particular, product G1 yielded values consistently lower than the other three products. Note however that the $ECD_{max} \pm 1$ stage values result in greater differentiation among products. The $ECD_{max} \pm 1$ or 2 stages parameters are subject to the same caveat as MMAD ± 2 stages. The range specified must be controlled and for this reason the ECD_{max} of a reference product should be specified.

4. Conclusions

Based on individual results, not all sprays pass the USP/EP proposed single dose limits for MDIs. However, only product E1 would have required additional sampling to determine its compliance status as two of the first ten sprays were outside the recommended 75–125% limits. These sprays were discharged after rest periods of 6 and 16 h. Testing in this laboratory has shown that unprimed sprays may generally deliver less drug substance than primed sprays. The sampling scheme for the determination of compliance of products should include appropriate rest periods. The relevance of the incorporation of discharges after rest periods, for unprimed sprays, is supported by the dosing regimen of products. In the case of these beclomethasone products, a single dose is recommended every 6 h. Therefore, when used strictly in accordance with label instructions, the dose received is always that delivered after a rest period of at least 6 h. The concept of requiring that unprimed sprays be incorporated into dose delivery studies has been suggested elsewhere [18,19] and is again supported by the limited results obtained in this study. The current USP limits would appear to be appropriate for these products.

The SAS® and USP methods yield comparable MMADs for the products tested. These methods

will be used in future studies with other products to determine if this is generally the case.

W_{max} provided a minimum of useful information and its value for future product comparison is doubtful. Further product studies using other available drug substances are required to further evaluate the usefulness of the other parameters identified in this report.

All of the products tested have been supported by clinical studies. If the individual samples tested are representative of the lots used in those studies and if they reflect general product performance, the test results define a range of acceptability for particle size distribution of beclomethasone dipropionate MDIs.

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