Dosing Reproducibility from Experimental Albuterol Suspension Metered-Dose Inhalers

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INTRODUCTION

Generic albuterol metered-dose inhalers (MDIs) entered Canada's market several years ago and albuterol is now off patent in the United States. Even so, an ongoing debate surrounds the standards to be met by generic equivalents in the United States. Part of that debate has been fueled by an article published by Cyr *et al.* (1) from the Health Protection Branch (HPB), Canada's regulatory agency, which reported significant discrepancies between label claim and unit spray drug content emitted from some Canadian generic formulations, following canister storage in different orientations. That work, along with further research at HPB (2), led to a new set of draft guidelines for pressurized MDIs in Canada (3). These guidelines require manufacturers to prove that unit spray content uniformity is within specifications throughout canister life for *single* sprays delivered from each batch of products, after storage for different times in different orientations. If this cannot be achieved, HPB advises the inclusion of labeling to require valve priming (shaking and firing sprays to waste) immediately prior to patient use. According to HPB, valve technology and formulation improvements should be made which ensure retention of prime and accurate metering performance under in-use conditions. The United States Pharmacopeia (USP) have recently improved their requirements for dosage uniformity testing of MDIs so that dose averaging of 10 single sprays (4) is no longer permissible. The new requirements (5) effectively state that 90% of *recommended doses* must be within 75–125% of the label claim and outliers must be within ±35%. This places an effective limit on the relative standard deviation or coefficient of variation of emitted doses = 15%. A recommended dose of albuterol, however, is 2 sprays from an MDI, and USP testing does not require storage in different orientations or testing throughout canister lifetime. Although the latter is practiced by most MDI manufacturers during formulation development, release testing after storage in different orientations (3) would be a considerable additional burden, and testing single sprays as opposed to recommended doses is contentious. The following work was undertaken to answer two questions: (i) Is storage orientation really a problem with a well-dispersed formulation metered by a Bespak BK 356 inverted metering valve? and (ii) Can an alternative, easy-fill, non-prime retaining valve design, which improves contact between the formulation bulk and the metering chamber, be used to overcome problems? The presently marketed albuterol formulation is a suspension which creams on standing (the drug is less dense than the vehicle). This characteristic has been used to explain low-dose emissions seen after standing MDIs in the valve-down position [(2); even though the process of drug egress from the metering chamber is hindered by the presence of a tortuous path through a very small orifice, drug purportedly floats out of the valve, leaving a propellant-rich suspension in the metering chamber]. There is no obvious explanation for high-dose emissions, which have also been reported (2). The worldwide innovator product (Ventolin, Glaxo) employs a Bespak BK 300 inverted metering valve in the United States. The use of that valve, which contains some nylon components, is restricted by contract to the innovator. Bespak's BK 356 is an acetal resin version of the original with some engineering improvements. This valve is used globally by some generic manufacturers. Generics which do not employ this valve may have different prime-retaining characteristics. Similarly, some generic manufacturers may supply inferior suspension products with inherent tendencies toward erratic dosing.

MATERIALS AND METHODS

MDI Preparation

Suspension MDIs were prepared by weighing 2.1 mg oleic acid (puriss >97%; Fluka, Ronkonkoma, NY) and 20.9 mg micronized albuterol (Armstrong Pharmaceuticals, New Canaan, CT; >97% by number <5-μm diameter, following microscopic size analysis) into 19-mL anodized aluminum canisters (Presspart cut edge). CFC-11 (3.9 g; Dupont, Wilmington, DE) was added and 50-μl inverted metering valves [Fig. 1; BK 356, regular (V1), large-groove easy-fill (V2) and small-groove easy-fill (V3); Bespak Inc., Cary, NC] crimped in place (Pamasol 2005/10, Pfaffikon, Switzerland). CFC-12 (10.1 g; Dupont) was added through the valve via a pressure burette (Model 35B, Aerosol Laboratory Equipment, Walton, NY). This formulation provides a theoretical ex-valve dose of albuterol = 100 μg/50 μL. The marketed formulation differs with respect to the concentration of nonvolatile ingredients (the drug/surfactant ratio and the ex-valve dose are the same, but 100 μg is metered in 63 μL). The formulation also differs with respect to the particle size distribution of the suspended drug, which is micronized to a higher degree (smaller diameters) in the innovator formulation. A more concentrated suspension was chosen here because easy-fill valves were available only with 50-μL volumes and the increased suspension concentration and the larger particle size distribution produced more rapid creaming in pilot studies (a worst-case scenario). The formulation was easily dispersible on standing, forming a homogeneous suspension after a single canister inversion; in all respects other than its heightened creaming tendency, it appeared to be similar to the innovator formulation. Each MDI contained a nominal 200

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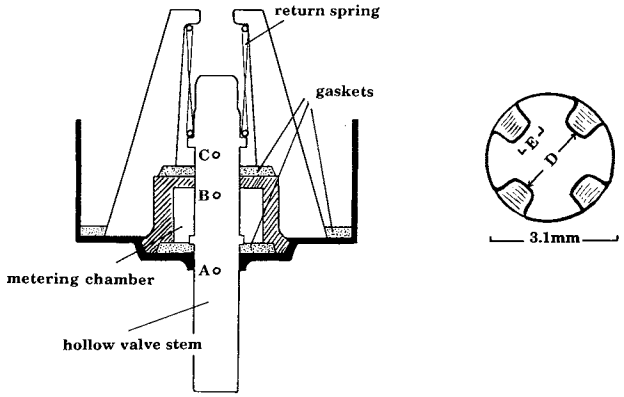

Fig. 1. Bespak 356 inverted metering valve (V1) shown diagrammatically. During actuation, depression of the valve stem causes isolation of the metering chamber by raising the orifice B, while the chamber empties through orifice A and the hollow portion of the valve stem. During filling, the suspension travels from the high-pressure bulk formulation through orifice C, the base of the valve stem, and out of orifice B, into the empty, low pressure, metering chamber. On the right is a diagram of a transverse section (looking from the inside of the canister) of the stem in the "easy-fill" valves (V2 and V3). In these, the stainless-steel valve stem between filling hole B and filling hole C was machined with four channels to enable flow between the metering chamber and the bulk of the formulation. The channels ended at a level equivalent to orifice B so that the metering chamber would remain isolated from the formulation following valve depression. The "easy-fill" valves V2 and V3 differed with respect to the size of the filling grooves. Dimension D was 2.1 and 2.3 mm with E = 1.0 and 0.75 mm (V2 and V3), respectively. In other respects, V2 and V3 were equivalent to a 50-μL BK 356.

doses. Mixing was performed immediately after manufacture (1 hr using a wrist-action shaker followed by 30 min of sonication). Testing was performed over a period of 28 days following manufacture.

Sample Collection

Single actuations were collected directly from the valve of individual canisters in a puff absorber using a standard procedure in this laboratory. Ex-valve testing was performed to avoid attributing variations in dose to variable actuator retention. The valve stem of each MDI to be tested was rinsed on all surfaces with HPLC-grade methanol and dried in a stream of filtered compressed air prior to and after testing. Canisters were weighed before and after sample collection to determine shot weights. The puff absorber was a stainless-steel receiver placed in a 100-mL beaker containing 40 mL 0.1 N NaOH as the collection liquid. A hole drilled in the top of the receiver provided a friction fit for the valve stem beneath the liquid surface. MDIs were inserted, valve stem down, into the hole, the valve was depressed for 1 sec, and the contents of the metering chamber were released and dissipated through the collection liquid. Albuterol was assayed spectrophotometrically at 243 nm after washing out the valve stem with 10 mL additional solvent and sonicating the "puff absorber" for 1 min to ensure dissolution and mixing.

Collection Scheme

Fifteen MDIs were tested. Five were equipped with regular BK 356 valves, five with large-groove easy-fill valves, and five with small-groove easy-fill valves (V1, V2, and V3, respectively; Fig. 1). The valves of all MDIs were primed prior to testing by firing 5 shots to waste through an oral actuator. Sixty seconds was allowed to pass between each of these shots. An 8-sec, 16-shake agitation was used immediately before each shot with the container held inverted, unless stated otherwise. Single actuations were collected according to seven separate firing protocols. These are summarized in the footnotes to Tables I and II. Values for n = 5 in these tables were generated by testing five MDI units in each case. Thus, the data in Table I were generated by collecting 15 separate shots from 15 MDIs. The data in Table II were generated by collecting 1 shot (S1) from each MDI according to each firing protocol (storage orientations and delays are quoted in Table II). Shots S2–S4 were collected directly after S1 in each case, by shaking and firing with minimal delay, to assess the speed with which good metering behavior could be recovered. Each protocol (A, B, C, etc.) was separated by the 5-shot priming routine described above. To demonstrate the effect of creaming on dosing reproducibility, no shaking procedure was used *immediately prior* to collection of S1 in firing protocols A and B. In these cases, canisters were shaken and allowed to stand undisturbed in an inverted position for 30 sec or 24 h (A and B, respectively) prior to firing and sample collection. On completion of this experiment, with an oral actuator attached, shot weights were determined for each MDI by firing 10 times, weighing and shaking the canister–actuator combination in a valve-down position between firings.

RESULTS AND DISCUSSION

The problem of erratic first-spray drug content in Cana-

Table I. Target and Average Doses (μg of Albuterol), Shot Weights (mg of Formulation), and Suspension Concentrations (% Albuterol by Weight) Emitted from V1, V2, and V3 Metering Under Ideal Testing Conditions (No Delay Between Shaking and Firing)[a]

	Target	V1	V2	V3
Average dose (μg)	100.0	108.5 (4.6)^0	46.6 (62.9)^5	48.8 (21.8)^5
Average shot weight (mg)	67.0	70.7 (2.9)^0	48.2 (42.0)^2	49.8 (18.6)^4
Average concentration (%, w/w)	0.149	0.154 (4.7)^0	0.082 (57.3)^5	0.097 (5.2)^5

[a] Valves were primed by shaking and firing to waste. Individual shots were then collected from five canisters by shaking and firing into the puff absorber. Coefficients of variation (%; n = 5) are in parentheses. Superscripts show the number of determinations which deviated by >25% from the target value.

Table II. Average Emitted Doses [μg of Albuterol (±Coefficient of Variation, %; n = 5)] Following Canister Storage in Different Orientations for Different Times (S1)[a]

	Firing protocol[b]							
	A (V1)[c]	B (V1)	C (V1)	D (V1)	E (V1)	F (V1)	C (V2)	C (V3)
S1[d]	87.5 (12.7)[1]	49.5 (22.4)[5]	81.3 (6.5)[0]	106.4 (9.6)[0]	94.9 (4.0)[0]	97.6 (6.1)[0]	60.2 (8.3)[5]	61.4 (36.6)[4]
S2	95.3 (8.4)[0]	63.0 (29.2)[2]	104.0 (5.5)[0]	102.4 (3.9)[0]	95.7 (2.5)[0]	94.9 (4.0)[0]	68.7 (8.2)[5]	54.2 (54.8)[5]
S3	100.1 (5.4)[0]	91.1 (9.7)[0]	98.4 (5.3)[0]	94.8 (9.2)[0]	87.9 (4.0)[0]	95.1 (4.6)[0]	36.0 (55.7)[5]	72.4 (2.1)[5]
S4	104.6 (6.1)[0]	91.6 (9.9)[0]	95.1 (3.0)[0]	90.7 (6.0)[0]	90.5 (4.6)[0]	95.1 (7.1)[0]	52.9 (40.8)[5]	72.7 (4.2)[4]

[a] Values are also presented for three further shots (S2, S3, S4), separated from S1 by shaking and firing without delay, to show the speed with which good metering behavior was recovered after storage. More than 1 min elapsed between each of S1, S2, S3, and S4. Superscripts show the number of determinations which deviated by >25% from the target value.

[b] Firing protocol for collection of S1. (A) Prime valve, shake, stand for 30 sec valve-down, fire. (B) Prime valve, shake, stand for 24 hr valve-down, fire. (C) Prime valve, shake, stand for 24 hr valve-down, shake, fire. (D) Prime valve, shake, stand for 24 hr valve-up, shake, fire. (E) Prime valve, shake, stand for 24 hr valve immersed sideways, shake, fire. (F) Prime valve, shake, stand for 24 hr valve in headspace sideways, shake, fire.

[c] Valve number.

[d] Shot 1 for valves V2 and V3 following firing protocol A gave values of 62.6 μg (±48.0%) and 70.1 μg (±14.4%), respectively. Shots 2, 3, and 4 (firing protocol A) were not determined for containers equipped with these valves.

dian generics (2,3) may be due to several factors. The albuterol suspension formulation in CFC propellants is a formulation which creams because the suspended drug is less dense than the propellant blend. The rate of creaming is a function of the particle size distribution in suspension and its rate of flocculation; larger particles and flocs cream most rapidly. It is known that rapid creaming can be manifested as low dose emissions as the delay between shaking and firing is increased (6). Thus, crystal growth (7), particle aggregation during storage, inadequate micronization, and poor deaggregation during manufacture (8) may all contribute to this problem. The design of the valve and its manufacturing materials may also interact in different ways with different formulations, and it is not mandatory, indeed it is impossible in this case, for generic manufacturers to copy the packaging of the innovator precisely. The questions asked in this paper relate only to the dosing uniformity of a creaming albuterol suspension packaged with Bespak BK 356 valves and some modified versions of these valves. Pilot studies in these laboratories with this and similar formulations (9) have shown that good dosing reproducibility is perfectly possible with the Bespak BK 356 valve tested under typical compendial testing conditions (5,9). Ex-valve testing, while not compendial in the United States, was chosen here because it avoids the complications associated with ex-mouthpiece testing due to variable actuator retention (9). The data presented for valve V1 in Table I shows excellent reproducibility. In both Table I and Table II, coefficients of variation [CV = (standard deviation × 100)/mean] refer only to the reproducibility of the measurements. In the event that the average dose is equal to the nominal or target dose (100 μg), a coefficient of variation <15% would imply that the product conformed to compendial standards. However, as the average dose deviates from the target, CV must also decrease for the product to continue to conform to standards (in the extreme, CV must tend to zero as the average dose → 75 or 125 μg). For this reason, even though the sample number is small, the number of observations showing deviations >25% from the target are shown as superscripts in Tables I and II. Superscript values of 1 or greater would fail compendial specifications.

The metering chamber of the regular BK 356 valve fills immediately after firing, following return of the valve stem to its resting position (Fig. 1). During firing, with the valve stem depressed, the chamber discharges to the atmosphere via orifice A, and orifice B is sealed. When the stem is released, the valve appears as it is shown in Fig. 1. Orifice A is sealed and B and C are in contact with the canister contents. In the valve-down position, immediately after firing, the pressure in the empty metering chamber is lower than the vapor pressure of the propellants in the canister and the metering chamber fills. Clearly, the nature of the suspension closest to the valve at that stage will define the drug content in the metering chamber. Tables I and II and Fig. 2 show the excellent performance characteristics of the unmodified BK 356 with this formulation. Shot weights were extremely reproducible and there was no tendency for drug to be dispensed in unusually low or high doses in the vast majority of cases. It was only following storage in the valve-down position (S1 and S2, firing protocol A and B; Table II) that the suspension which the valve was metering became drug deficient (shot weights for S1, protocol B = 69.7 ± 0.8 mg). These lower emitted doses after valve-down storage show quite clearly that albuterol can float out of the valve, despite the rather tortuous path through orifices B and C. When this suspension is allowed to stand for 24 hr packaged in glass, however, creaming is complete. Thus, the fact that albuterol is still emitted in Shot 1 of protocol B (Table II) is some indication of the difficulty with which the suspensoid leaves the metering chamber when a liquid bridge exists through which particles can move. If the bridge existed sideways (protocol E, canister more than half full; Table II), suspension separation was not a problem, although it should be noted that the orientation of the valve stem orifice (C; Fig. 1) was uncontrolled and unknown in this test. If no bridge existed, this valve held its prime for at least 24 hr and albuterol was accurately metered (protocols D and F; Table II).

Firing protocols A, B, and C are of further interest from

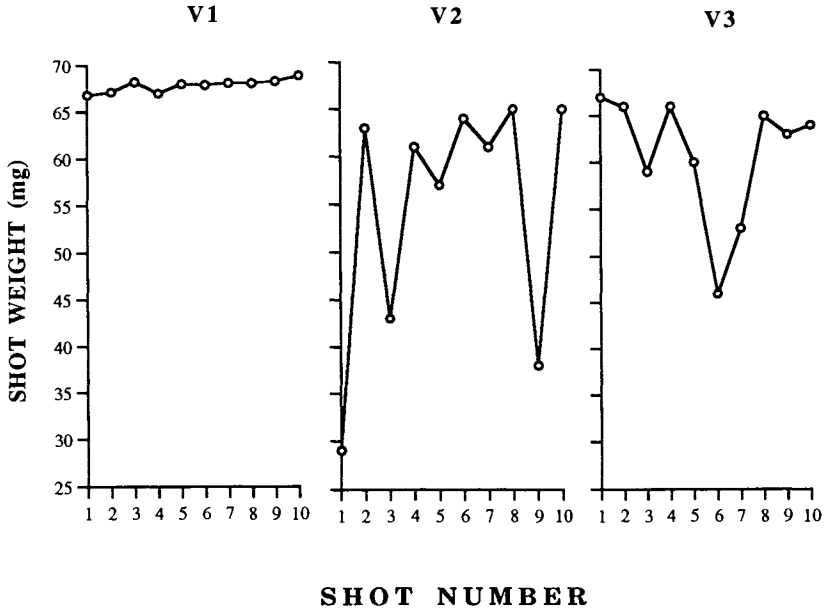

Fig. 2. Typical shot weight versus shot number plots for valves V1, V2, and V3 metering an identical albuterol formulation.

a regulatory point of view. Protocol B was the only case in which this formulation would likely fail to meet compendial specifications for dosage uniformity (90% of the values for the sum of S1 and S2 must be within 25% of the target). However, protocol B requires product misuse because no shaking was used prior to the collection of Shot 1. When shaking was employed (protocol C), although S1 was low, there were no doses below 76 μg and the valve refilled from a well-mixed suspension to give a good measure for S2. Protocol A passed compendial specifications but failed the single-shot reproducibility criterion imposed by HPB. Even so, this protocol also entails product misuse in that a delay of 30 sec between shaking and firing an MDI is beyond anything envisaged during normal use. It appears, therefore, that the new Canadian guidelines requiring this type of testing as product *release* tests (3) may be unnecessarily stringent for a product shown in formulation development and stability trials to display these characteristics.

At the outset of this trial the performance of the BK 356 (V1) was expected to be somewhat worse when the valve was coupled to this particular formulation (known to cream more rapidly than its less concentrated, marketed counterpart). Because of this, V2 and V3 were also tested. Although these valves were not designed to hold their prime, the large cross-sectional area available for product entry and exit into the metering chamber was expected to enable the metering chamber to be filled rapidly upon shaking. This would preclude the need for prime retention between doses. Figure 2 and Tables I and II show that these valves gave highly variable shot weights and dosing performance with this formulation. For unknown reasons, in early doses, drug was emitted at low concentrations [doses increased as the canisters emptied and there was no drug retention in the empty canisters (Table I, V2 and V3)]. These results indicate the difficulty associated with the design of rapid-fill metering valves. An increased amount of shaking failed to improve the performance of V2 or V3 with this formulation. Fifty microliters may not seem to be a large volume to fill, but that volume appears to fill much more reproducibly when a pressure difference is applied over a small channel rather than a large one. Indeed, shot weight variability decreased as the cross-sectional area available for filling decreased (area ranks V2 > V3 > V1; Fig. 2). Although this simple explanation seems plausible, it should also be emphasized that valves V2 and V3 use filling grooves, while V1 uses a true orifice (Fig. 1). The excellent results seen with the unmodified BK 356 with this formulation are a good indication that the technology already exists to ensure the metering performance that the Canadian HPB wish to see proven for all products (3). There is probably a need within the industry, however, to recognize the importance of increased testing of this type to ensure, during formulation development, that the final product meters drug reproducibly at the patient interface.

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REFERENCES

1. T. D. Cyr, S. J. Graham, K. Y. R. Li, and E. G. Lovering. Low first-spray drug content in albuterol metered dose inhalers. *Pharm. Res.* 8:658–660 (1991).
2. S. J. Graham, E. D. Ormsby, and E. G. Lovering. Single spray drug content in a metered dose aerosol formulation and a collection scheme for content uniformity. *Pharm. Forum* 18:4400–4403 (1992).

3. Bureau of Human Prescription Drugs. *Draft Guidelines for Metered-Dose Inhalers,* Health Protection Branch, Vanier, Ontario, Nov. 1992.
4. United States Pharmacopeia XXII. ⟨*601*⟩ *Aerosols,* USP Convention, Rockville, MD, 1990, pp. 1556–1557.
5. United States Pharmacopeia XXII. ⟨*601*⟩ *Aerosols and* ⟨*905*⟩ *Uniformity of Dosage Units,* Supplement 7, USP Convention, Rockville, MD, 1992, pp. 3122–3129, 3146–3148.
6. R. N. Dalby. Special considerations in the formulation of suspension type metered dose inhalers. *Aerosol Age* Oct.: 22–89 (1990).
7. E. M. Phillips, P. R. Byron, and R. N. Dalby. Axial ratio measurements for early detection of crystal growth in suspension-type metered dose inhalers. *Pharm. Res.* **10**:454–456 (1993).
8. P. R. Byron. Aerosol formulation, generation, and delivery using metered systems. In P. R. Byron (ed.), *Respiratory Drug Delivery,* CRC Press, Boca Raton, FL, 1990, pp. 168–205.
9. E. M. Phillips, P. R. Byron, K. Fults, and A. J. Hickey. Optimized inhalation aerosols. II. Inertial testing methods for particle size analysis of pressurized inhalers. *Pharm. Res.* 7:1228–1233 (1990).