ELSEVIER

International Journal of Pharmaceutics 139 (1996) 255–256

international journal of pharmaceutics

Rapid communication

Comparison of aerodynamic particle size from 250 μg per dose beclomethasone dipropionate metered-dose inhalers

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Received 30 March 1996; accepted 24 April 1996

Abstract

A high performance multistage liquid impinger was used to evaluate the aerodynamic particle size distribution of beclomethasone dipropionate metered-dose aerosols (250 μg per dose) available in the UK. These were: *Becloforte*, marketed in the UK by Allen and Hanburys, (3 batches); *Becloforte* imported from Spain as a parallel import by Dowelhurst (1 batch); *Beclazone 250*, Norton Healthcare (3 batches); and *Filair Forte*, 3M Health Care (2 batches). There were no significant differences among the different products in terms of the combined mass of drug deposited at Stages 3 and 4 (< 6.8 μm). The deposition on Stage 4 (< 3.1 μm) followed the order *Becloforte* (UK or Spanish origin) > *Beclazone 250* > *Filair Forte*. Only the result for *Filair Forte* reached significance.

Keywords: Aerodynamic particle size; Beclomethasone dipropionate; High performance multistage liquid impinger; Metered-dose inhaler

There are currently two brands of generic beclomethasone dipropionate (BDP) metered-dose inhaler available in the UK (*Beclazone*, and *Filair*) in addition to the original product (*Becotide*/*Becloforte*). However, there has been controversy as to the equivalence of the generic products (Crompton and Prowse, 1994).

The aerodynamic particle size of an inhaled drug is important in determining its penetration to the site of action in the lung. The particle size distribution of drug emitted from metered-dose aerosols may be determined by inertial impingement techniques, such as the high-performance multistage liquid impinger (HPMLI; Aiache et al., 1993). This enables particles to be determined in four fractions of aerodynamic particle size (> 13,

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PII S0378-5173(96)04572-3

13–6.8, 6.8–3.1, < 3.1 μm). The third and fourth stages of the impinger (< 6.8 μm) collect the potentially respirable fraction. Coarse material (> approximately 25 μm) is collected at a right-angled connection between the inhaler and impinger (known as the throat).

This study describes a comparison of the aerodynamic particle size distributions of BDP from the 250 μg/dose metered-dose inhalers available in the UK. The effect of batch to batch variation was also assessed.

A high-precision multi-stage liquid impinger (HPMLI, Copley Instruments) operated at 60 l/min was used for the determination of aerodynamic particle size distribution, with methanol (20 ml) in each of the impingement chambers.

The beclomethasone dipropionate 250 μg per dose inhalers were *Becloforte* (Allen and Hanburys, Uxbridge, UK), *Beclazone 250* (Norton Healthcare, Harlow, UK) and *Filair Forte* (3M Health Care, Loughborough, UK). Three batches each of *Beclazone 250* and *Filair Forte* were tested. In the case of *Becloforte*, four batches were tested: three of UK origin, and one of Spanish origin which was imported to the UK by Dowelhurst, Warwick, UK. Five inhalers were tested from each batch.

The tested inhaler was shaken for 30 s and two activations discarded to waste. A further ten activations were discharged into the inlet of the HPMLI. There was a minimum 5-s delay between activations, during which the inhaler was gently agitated. Since the mouthpiece of the *Filair Forte* inhaler was a poor fit in the standard rubber inlet adapter, a silicon rubber adapter with the correct profile, supplied by 3M Health Care, was used with this product.

Each component was washed with methanol to recover the drug and diluted to give solutions for analysis in methanol:water (85:15), containing 14 μg/ml biphenyl (internal standard). Analysis was by high-performance liquid chromatography (HPLC), using a 100 x 4.6 mm 5 μm Spherisorb ODS2 column maintained at 30–32°C, a mobile phase of methanol:water (85:15) at a flow rate of 1.5 ml/min, injection volume of 100 μl and ultraviolet detection at 240 nm. Quantification was by peak area, using a standard curve, prepared daily.

Statistical evaluation of the results was by nested analysis of variance, with pair-wise comparison by t-test, where appropriate ($P = 0.05$).

The mean day to day recovery of BDP ($n = 4$), spiked into the various components of the inhaler and impinger, at typical levels found on testing, was in the range 99–103% of the theoretical values. The precision was less than 5% relative standard deviation (RSD). The only exception was in the case of Stage 1 of the impinger, spiked at levels of 39–47 μg BDP. In this case, mean recovery was 109% (6.8% RSD). During testing, the temperature was in the range 18–21°C and the relative humidity was in the range 33–43%.

One of the batches of *Filair Forte* studied gave a very low deposition at Stages 4 and 3 + 4. Further investigation with the same samples (personal communication, 3M Health Care) using the BP test for deposition confirmed the low results in the potentially respirable range in the same samples, but other samples from the same batch gave higher results. In view of the unexplained discrepancy between these samples, the results from this batch are not presented.

The Spanish version of *Becloforte*, which is licensed for use in the UK as a parallel imported product, had a metal can which was visually identical to the UK version, but only contains 180 doses, compared to 200 doses for all the other products studied. The actuator was similar in appearance to that of the UK version, but was not identical. A single batch of this product was therefore tested in order to compare it to the UK version.

There were no significant differences among different batches of the same product in deposition at Stages 3 or 3 + 4, although there was a significant difference between batches at Stage 4. However, the individual batch means differed at each stage by less than 4 μg from the corresponding overall product means.

There was no significant difference among the four products (Table 1) in terms of the mass of potentially respirable BDP deposited (Stages 3 + 4). At Stage 4, there were no significant differences among *Becloforte* (UK), *Becloforte* (Spanish) or *Beclazone 250. Filair Forte* had significantly lower deposition at this stage than all of

Table 1
Mean (± standard deviation) deposition of BDP from inhalers, as μg — pooled results

Product	Becloforte(UK)	Becloforte(Spanish)	Beclazone250	FilairForte
n	15	5	15	10
Actuator + valve stem	22.0 (2.6)	27.5 (3.8)	27.7 (2.8)	39.9 (16.5)
Throat	136.3 (8.0)	148.0 (9.6)	127.5 (16.1)	112.1 (20.3)
Stage 1	3.4 (0.7)	3.7 (0.9)	4.8 (1.1)	7.8 (6.7)
Stage 2	15.0 (2.8)	13.0 (0.9)	21.7 (4.6)	20.8 (2.2)
Stage 3	56.5 (4.2)	59.6 (1.8)	58.8 (5.8)	63.3 15.3)
Stage 4	33.1 (5.0)	38.8 (4.7)	30.0 (4.4)	20.3 (3.1)
Stage 3+4	89.5 (7.3)	98.4 (5.0)	88.8 (9.0)	83.6 (13.9)
Mean of total recovered per actuation / μg	266.2 (11.6)	290.6 (6.9)	270.6 (11.6)	264.1 (22.3)

the other products. *Filair Forte* gave significantly higher deposition at Stage 3 than *Becloforte* (UK) or *Beclazone 250*; *Becloforte* (Spanish) was not significantly different to any of the other products studied.

Although a particle size of less than approximately 6 μm is required for penetration of drug to the peripheral areas of the lung, the optimum is approximately 2 μm (Hickey, 1992). It has therefore been suggested that the proportion of drug on Stage 4 (< 3.1 μm) is of importance in determining the therapeutic efficacy of a BDP metered-dose inhaler (Kenyon et al., 1995). The proportion of the dose at Stage 4 was in the order *Becloforte* (Spanish) > *Becloforte* (UK) > *Beclazone* > *Filair Forte*. The proportion at this stage was 10% less for *Beclazone* 250 than for *Becloforte* (UK). For *Filair Forte*, there was 37% less.

Kenyon et al. (1995) also investigated single batches of different BDP MDIs with the same type of impinger. They obtained similar results for the proportion of drug deposited at Stage 4 to those reported here. However, these authors obtained lower results for Stage 3. The overall proportion of the dose in Stages 3 + 4 were in the range 23–24% for each of *Becloforte*, *Beclazone* 250 or *Filair Forte*, compared to values of 32–34% reported here. The British Pharmacopoeia (1994) specification for 250 μg per dose BDP MDIs is for the dose at less than 6.4 μm (determined using the twin-impinger) to be not less than 25% of the emitted dose. The results from HPMLI (Stages 3 + 4, < 6.8 μm) and twin-impinger (Stage 2, < 6.4 μm) would be expected to be in good agreement (Aiache et al., 1993). The data reported here are therefore in accordance with expected values, but those from Kenyon et al. (1995) are incompatible with them and may denote a methodological problem.

In conclusion, no differences were found between the inhalers in terms of the potentially respirable mass (< 6.8 μm), but differences were observed in the fine particle fraction (< 3.1 μm). The clinical significance of this in asthmatic patients requires further investigation.

Acknowledgements

The HPMLI was lent by Norton Healthcare. Prof. H. Chrystyn and staff at 3M Health Care and Norton Healthcare are thanked for valuable advice and assistance.

References

Aiache, J.-M., Bull, H., Ganderton, D., Haywood, P., Olsson, B. and Wright, P., Inhalations: collaborative study on the measurement of the fine particle dose using inertial impactors. *Pharmeuropa*, 5 (1993) 386–389.

British Pharmacopoeia 1993, *Addendum 1994*, HMSO, London, 1994, pp. 1408–1410.

Crompton, G.K. and Prowse, K., Matching inhalers and spacer devices. *Br. Med. J.*, 309 (1994) 1584.

Kenyon, C.J., Dewsbury, N.J. and Newman, S.P., Differences in aerodynamic particle size distributions of innovator and generic beclomethasone dipropionate aerosols used with and without a large volume spacer. *Thorax*, 15 (1995) 846–850.

Hickey, A.J., Summary of common approaches to pharmaceutical aerosol administration. In Hickey, A.J. (Ed.), *Pharmaceutical inhalation aerosol technology*, Marcel Dekker, New York, 1992, pp. 255–288.