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Drug delivery characteristics of Bricanyl Turbohaler™ dry powder inhalers

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Abstract

The Turbohaler™ is the one multidose reservoir type dry powder inhaler (DPI) with significant clinical usage but there is little information on the precision of its single dose delivery characteristics. The single dose delivery efficiency of terbutaline sulphate (nominally 500 μg) from two batches of Bricanyl Turbohalers™ (11 and 59 devices) has therefore been studied at air flow rates of 28–30 and 60 l min^{-1} which are clinically relevant test conditions for this DPI. At 60 l min^{-1} statistically significant differences both within and between batches were obtained for emitted dose (±SD, $n = 110, 130$), 421 ± 73, 387 ± 58 μg and fine particle dose (0.5–6.4 μm MMAD), 249 ± 41, 214 ± 44 μg. These data imply an emitted dose range of ±50% and a fine particle dose range of ±70% from this DPI system. Through-life total dose emission in terms of the average values remain consistent. Reducing air flow rates to approx. 30 l min^{-1} lowered the mean emitted dose by about one third with the clinically important fine particle dose being reduced 3-fold to 59 ± 25 μg; this underlines the likely sensitivity of effective delivery, to patients' lung function. These results reinforce the need to provide single dose data at clinically relevant flow rates in the assessment of DPI performance. Expressing data as mean performance for a cumulative series of dose units smooths down this single dose variability by a factor of two.

Keywords: Aerosol; Dry powder inhaler; Turbohaler™; Terbutaline sulfate delivery efficacy

1. Introduction

Inhalation devices for the treatment of asthma include nebulisers, pressurised metered dose inhalers (PMDIs) and dry powder inhalers (DPIs); of these, PMDIs are the most widely prescribed. However, there is increasing interest in DPI technology which involves particle cloud generation as a result of the patient drawing air through the device and so fluidising a powder bed containing drug. This avoids the need for propellants and addresses the clinical problem of co-ordination of breath inspiration with PMDI device actuation which can be experienced by some 30–50% of patients (Crompton, 1987; Drepaul et al., 1989).

DPI systems currently licensed in Europe fall into two categories based on dose loading. The first involves factory allocation of unit doses as capsules or blisters, e.g., Spinhaler™ (Fisons), Rotahaler™ (Glaxo), Cyclohaler™ (Du Pont Pharma) Inhalator™ (Boehringer-Ingelheim) and Diskhaler™ (Glaxo). Turbohaler™ (Astra),

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Pulvinal™ (Chiesi, available only in Denmark) and Easyhaler™ (Orion, licensed in Finland) are multi-dose reservoir systems incorporating a dose metering unit fed from a reservoir of bulk powder formulation and charged by a patient actuation manoeuvre. As demonstrated by the patent literature, there is considerable activity in the development of such truly multi-dose devices which contain up to 200 drug doses.

However, since drug delivery from DPIs is a combined function of dose metering, drug emission from the device and particle size quality of the aerosol cloud, it is clear that reservoir type devices present the greater challenge to the design of DPI systems with good dose delivery characteristics. Because Turbohaler™ is currently the only licensed reservoir device with significant clinical usage, we have examined its single dose delivery performance for terbutaline sulphate in order to provide in vitro base-line comparison data for other multi-dose DPI systems in development. Studies were carried out at through-device flow rates of 60 or 28–30 l min^{-1} which are pertinent to Turbohaler™. Adult patient cohort mean values of peak inspiratory flow rate (PIF, l min^{-1}) achievable through Turbohaler™ are: 59, range 25–93, $n = 101$ (Engel et al., 1990), 60, range 26–103, $n = 103$ (Brown et al., 1991) and 64, range 25–110, $n = 33$ (Fahy et al., 1992). Pedersen et al. (1990) have reported that children aged 6 years and above can generally achieve PIFs ≥ 30 l min^{-1} through this DPI.

2. Experimental

2.1. Materials

2.1.1. Terbutaline sulphate

Terbutaline sulphate (Sigma Chemical Co.) was of 99.9% purity; a single sample was used as the analytical standard throughout; the material was held in a desiccator, protected from light, at ambient temperature and used as received.

2.1.2. Bricanyl Turbohaler

Two lots designated E and K, nominally containing 200×500 μg doses of terbutaline sulphate, were obtained commercially. The majority of the work was carried out using lot K; drug samples taken from two devices assayed at 100.3 and 100.5% against the analytical standard (HPLC). Lot E was used to establish degree of replication and evaluate comparative batch performance.

2.1.3. HPLC reagents

Propan-2-ol (BDH) and ammonium acetate (Fisons) were HPLC grade; glacial acetic acid (BDH) was AR grade; water was freshly distilled.

2.2. Methods

2.2.1. HPLC determination of terbutaline sulphate: chromatographic conditions

The following conditions were employed: column, 250×5 mm Apex CN RP 5 μm (Jones Chromatography); mobile phase, propan-2-ol (20), 1.0 M aqueous ammonium acetate (75), distilled water (to 1000) adjusted to pH 4.0 with glacial acetic acid; flow rate, 1.9 ml min^{-1}; temperature, ambient; detection, 280 nm at 0.01 AUFS; injection volume, 100 μl; concentration, typically 2–6 μg ml^{-1}; retention time, typically 3.5 min.

2.2.2. Linearity and reproducibility

Duplicate calibration plots were linear over the range 2–10 μg ml^{-1} (RSD slopes, 1.3, 0.7%; correlation coefficients, 0.9998, 0.9999) and passed through the origin (SD > intercept). 10 replicate injections at 2.0 and 5.0 μg ml^{-1} had 95% confidence limits of ± 0.41 and ± 0.57% respectively.

Terbutaline sulphate was determined by bracketing samples with standards; values reported were calculated from standard response factors without applying 'purity corrections' which were negligible.

2.2.3. Delivery of terbutaline sulphate from Turbohalers™

2.2.3.1. Emitted dose and fine particle fraction at 60 l min^{-1} flow rate. This was determined using Apparatus A (BP 1993, Appendix XVIIC), a glass twin-stage impinger (TSI) calibrated at a flow

rate of 60 ± 5 l min^{-1}; particles with mass median aerodynamic diameter (MMAD) 0.5–6.4 μm are trapped in stage 2. The emitted dose is defined as the total amount of drug delivered to the TSI under the experimental conditions; the fine particle fraction is the mass of drug deposited in stage 2 expressed as a percentage of the emitted dose.

There is a significant resistance to flow through the Turbohaler™ (pressure drop 3.6 kPa, SD 0.1, $n = 10$) at an exit (mouthpiece) flow rate of 60 l min^{-1}. Consequently, it was necessary to set the flow rate with the Turbohaler mounted in the TSI 'throat' via an elastomeric adaptor; stage 1 and 2 chambers were charged with 7 and 30 ml HPLC mobile phase, respectively. The Turbohaler™ was loaded in the vertical position, inserted into the TSI, fired by switching on the pump for 10 s and leaving the device in situ for 60 s after switching off the pump. The TSI was then broken down and its total contents rinsed into a 100 ml volumetric flask with HPLC mobile phase and adjusted to volume before assaying for drug content by HPLC. Alternatively, the contents of stage 2 and the combined contents of the throat and stage 1 were rinsed into separate 50 ml volumetric flasks to allow estimation of both emitted dose and fine particle fraction for the same shot.

2.2.3.2. Emitted dose and fine particle fraction at 28.3 l min^{-1} flow rate. This was determined using an eight-stage, Mark II Andersen Sampler (Grazeby-Andersen Samplers, Atlanta, GA) fitted with a preseparator containing 5 ml methanol to remove large particles, after-filter and TSI throatpiece as entry port. To minimise particle 'bounce' and consequent de-aggregation which can bias fractional deposition estimation, the impinger plates were pre-coated by dipping into a solution containing Span 85 (1.0%) in hexane (AR grade) and air dried. The greater number of collection stages together with assay sensitivity limit prohibited single shot determination; cumulative sequences of five shots were therefore fired into the Andersen before assay. This number was selected because the Turbohaler™ has five sets of six dosing holes and determination therefore represents the mean from one complete rotation of the loading mechanism. Preliminary experiments established the rinsing and analytical volumes for the stages and pre-separator (50 ml HPLC mobile phase) and that drug deposition on the after-filter was not detectable; this was not therefore routinely assayed. Drug deposition on the combined surfaces of the Turbohaler-throat adaptor, throat and the glass throat-sampler connector was also determined.

The Andersen pump was adjusted to draw air at 28.3 ± 0.5 l min^{-1} through the Turbohaler™ when fitted into the throat via the adaptor. Individual shots of the sequence were fired as for the TSI. Fine particle fraction was obtained by summing drug deposition on stages 2–7 (MMAD 0.4–5.8 μm) and calculating this as a percent of the emitted dose determined from total drug recovered.

2.2.4. Reproducibility of initial drug delivery within and between devices

Lot E: emitted dose and fine particle fraction were determined for each of shots 11–20 for 10 devices using the TSI; shots 1–10 were fired to waste to prime the device. Mouthpieces were wiped clean with a dry tissue following priming sequences.

Lot K: drug emission was determined for each of shots 1–5 using the TSI.

2.2.5. Through-life dose metering efficacy

Three sequences of five single shots representing sampling from the beginning, middle and end of the device use-life (shots 11–15, 91–95, 181–185) were collected into the TSI; 10 replicate devices were evaluated. Intermediate shots were fired to waste using the standard TSI protocol.

3. Results and discussion

3.1. Emitted dose at 60 l min^{-1}

Previous reports (Wetterlin, 1988; Newman et al., 1989; Bell, 1992) do not provide a clear indication of single shot variability between and within Bricanyl Turbohalers™. The first objective in

Table 1
Single shot data for terbutaline sulphate emitted from Bricanyl Turbohalers™

Turbohaler lot K: shots 1–15						Turbohaler lot E: shots 11–20				
TBH code	Shot no.	Emitted dose (μg)			Statistic	TBH code	Emitted dose (μg)			Statistic
		Mean	(±SD)	Range			Mean	(±SD)	Range	$t_{11-15/16-20}$
K1	1–5	398	(±52)	332–453		E1	427	(±88)	259–518	1.04
	6–10	403	(±102)	289–542	$F = 0.01$	E2	430	(±41)	371–509	0.33
	11–15	397	(±42)	363–465	$p = 0.989$	E3	473	(±48)	386–523	1.23
	1–10	401	(±76)	289–542	$t_{1-10/11-15} = 0.76$	E4	400	(±55)	324–507	1.06
	1–15	400	(±65)	289–542		E5	402	(±95)	231–523	0.25
						E6	383	(±91)	226–523	1.41
K2	1–5	389	(±56)	344–485		E7	429	(±63)	321–517	0.97
	6–10	407	(±86)	269–486	$F = 0.18$	E8	447	(±72)	353–583	1.82
	11–15	412	(±77)	308–528	$p = 0.841$	E9	366	(±75)	221–487	0.99
	1–10	398	(±69)	269–486	$t_{1-10/11-15} = 1.03$	E10	449	(±62)	333–523	1.95
	1–15	404	(±70)	269–528		E11	429	(±62)	330–509	0.51
						Mean values				
						all shots	11–15: 418 (±67)			0.51
							16–20: 425 (±78)			
							11–20: 421 (±73)			
						device mean	421 (±31)			anal. var.
						all shots	devices E1–E11			$F = 1.94$, $p = 0.048$
						all shots	devices E1, E2, E4–E11			$F = 1.38$, $p = 0.21$
						shots 11–15	devices E1–E11			$F = 0.47$, $p = 0.90$
						shots 16–20	devices E1–E11			$F = 2.86$, $p = 0.008$

Air flow rate 60 l min^{-1} through devices.

this study was therefore to examine the efficacy and reproducibility of dose loading and emission.

Because of cautionary experience with PMDIs, priming of Turbohalers™ by firing shots 1–10 to waste was adopted for lot E devices, shots 11–20 being evaluated. A subsequent examination of shots 1–15 from two lot K devices showed variation in delivery to be random with no obvious

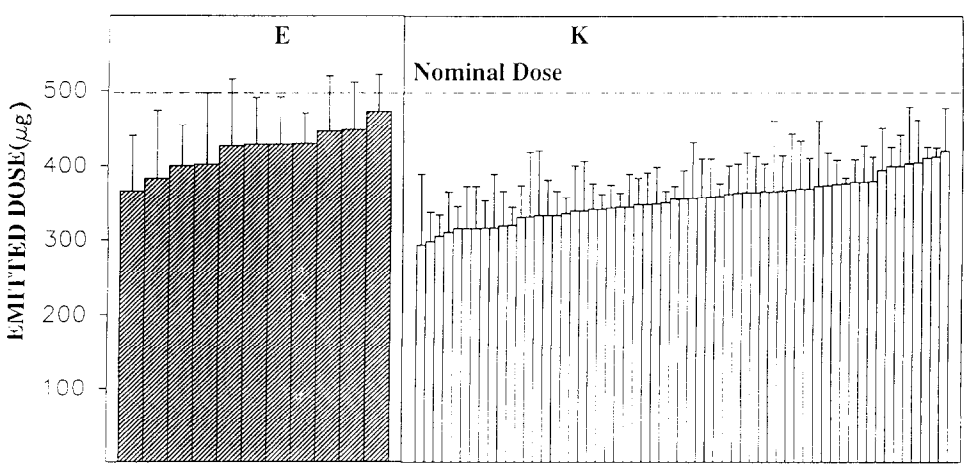

Fig. 1. Mean dose of terbutaline sulphate emitted per Turbohaler™ device (bars are standard deviations). Lot E, 10 shots (11–20); lot K, 5 shots (1–5). Ordinate: emitted dose (μg).

trends or significant difference between the 'priming shots' (1–10) and shots 11–15 when examined by t-test and analysis of variance (Table 1). Similar conclusions were reached with regard to fine particle (0.5–6.4 μm) dose and fraction (Tables 4 and 5). Device priming was therefore normally omitted in subsequent work. The single shot data given in Table 1 also show there was no significant difference between the mean values for shots 11–15 and 16–20 whether assessed for individual devices, on device means or for individual shots ($t \leq 1.82$). Subsequent studies with lot K therefore involved sequences of five shots.

Fig. 1 and 2 illustrate dose emission from the two batches on a per device and total shot basis, respectively. The data in Fig. 1 have been ranked to illustrate the range of device performance. In Fig. 2 the total shot data derived from 'initial' values for the 59 lot K devices of Fig. 1 have been supplemented by values from other Turbohalers™ where three-shot sequences were available. Mean emitted dose ($\pm$SD) calculated on either basis was essentially the same although standard deviations for total shot analysis doubled (lot E, 421 $\pm$ 31, 421 $\pm$ 73 μg; lot K, 385 $\pm$ 31, 387 $\pm$ 58 μg). These mean values equate to 84 and 77% nominal, respectively.

Fig. 2 indicates that terbutaline dose emission is normally distributed, confirmed by breaking down the more plentiful dose distribution data for lot K into smaller dose intervals; 5/385 doses were outside $\pm$3SD (161, 176, 583, 645, 860 μg) compared to 4/385 expected. Statistical comparison of the data was therefore made by analysis of

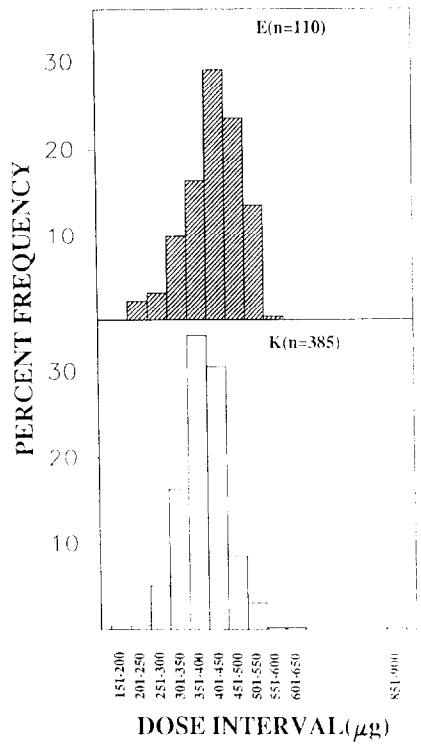

Fig. 2. Frequency distribution for single doses of terbutaline sulphate emitted from Turbohalers™ (air flow rate: 60 l min^{-1}). Ordinate, percent frequency; abscissa, dose interval (μg).

variance and t-test which indicated significant inter- and intra-batch variation (lot E, $F = 1.94$, $p = 0.048$; lot K, $F = 1.71$, $p = 0.003$; $t_{E/K}$ devices = 3.48, $t_{E/K}$ shots = 5.54). To check this finding was not due to sample size difference or analyti-

Table 2
Mouthpiece deposition of terbutaline sulphate in Bricanyl Turbohalers™

TBH code	Emitted dose (μg)		Mouthpiece deposition (μg)		Total drug [a] (μg)	
	Mean ($\pm$SD)	% nominal	Mean ($\pm$SD)	Range	Mean ($\pm$SD)	% nominal
K54	434 ($\pm$46)	87	44 ($\pm$12)	31–60	478 ($\pm$55)	96
K55	360 ($\pm$35)	72	56 ($\pm$29)	35–106	415 ($\pm$35)	83
K56	390 ($\pm$49)	78	68 ($\pm$26)	43–98	458 ($\pm$30)	92
K57	374 ($\pm$49)	75	59 ($\pm$21)	39–86	434 ($\pm$69)	87
K58	369 ($\pm$73)	74	69 ($\pm$34)	34–125	438 ($\pm$63)	88
Mean per device	385 ($\pm$29)	77 ($\pm$6)	59 ($\pm$10)		445 ($\pm$24)	89 ($\pm$5)

Air flow rate 60 l min^{-1} through device. Means are for five single shots per device.
[a] Total drug = emitted drug + mouthpiece deposition.

cal aberration over the 10 month study period, lot K data were chronologically assigned to five groups of 10 and one of nine DPIs. The spread of these group means was such that, whilst no inter-group difference was seen ($F = 1.11$, $p = 0.36$, $t \leq 1.91$), significant difference against lot E was maintained for 4/5 groups ($t = 1.25$ or ≥ 2.64).

Although our emitted dose delivery efficiencies of 84 and 77% nominal are close to the in vivo value of 86% reported by Engel et al. (1992), they differ from other reported impinger data of 68% (Bell, 1992) and 100% (Newman et al., 1989); the latter was obtained by 'normalising' raw data to a 500 μg base-line, however. Factors accounting for these discrepancies and deviations from nominal dose emission include shot collection methodology, intrinsic metering efficacy and drug retention within the device mouthpiece and body. Deposition on the external (patient wipeable) and internal parts of the mouthpiece were determined for five shots from each of five DPIs (Table 2). Values ranged from 31 to 125 μg per shot and it was also observed that build-up of powder on the surfaces of the inhalation channel and dosing hole plate occurred during through use-life testing. Occasional release of retained drug could account for the small number (11/1118, < 1%) of randomly occurring, high, emitted dose values obtained during all aspects of our studies using the standard TSI procedure and arbitrarily defined as ≥ 625 μg, 125% nominal. These were regarded as outliers (for lot K ≥ mean + 4SD) and omitted from any statistical analyses reported here. In each case, the following shot value fell with the normal range.

Turbohaler™ through-life emitted dose performance was evaluated at 60 l min^{-1} using devices K33–K42. The results and associated analyses of variance are shown in Table 3 and indicate that there was no change in Turbohaler™ dose emission distribution through-life.

3.2. Emitted dose at 28–30 l min^{-1}

This was studied since young children (< 6 years) and a small proportion of adult patients only achieve PIF values of ≤ 30 l min^{-1} through the device (Engel et al., 1990; Pedersen et al., 1990). The mean emitted dose per device found using the Andersen Sampler was 351 ± 56 μg (range 279–446 μg) which, in statistical terms, is

Table 3
Through-life delivery of emitted dose from Bricanyl Turbohalers™

TBH	Emitted dose (μg) at 60 l min^{-1}							
	Shots 11–15		Shots 91–95		Shots 181–186		AoV	All shots
	Mean (±SD)	Range	Mean (±SD)	Range	Mean (±SD)	Range	*F*	Mean (±SD)
K33	344 (±40)	278–375	334 (±28) [a]	312–374	310 (±45)	235–355	1.02	329 (±39)
K34	378 (±39)	320–430	339 (±53)	266–417	284 (±61)	191–341	3.90	327 (±64)
K35	338 (±59)	237–383	417 (±52)	334–469	426 (±35)	388–469	4.77 [b]	394 (±61)
K36	362 (±95)	263–518	392 (±88)	303–514	296 (±83)	169–360	1.54	350 (±92)
K37	397 (±102)	226–488	403 (±43)	341–441	374 (±124)	291–589	0.12	385 (±90)
K38	456 (±63)	361–513	430 (±41)	386–482	429 (±119)	252–537	0.18	438 (±76)
K39	373 (±34)	321–401	388 (±85)	255–479	368 (±31)	337–418	0.17	376 (±53)
K40	401 (±70)	289–460	336 (±47)	283–342	370 (±88)	300–523	1.07	369 (±71)
K41	439 (±63)	373–523	429 (±88)	387–507	385 (±50)	332–462	0.87	418 (±68)
K42	378 (±54)	305–432	350 (±102)	217–456	352 (±83)	224–453	0.83	350 (±82)
Mean	387 (±38)		382 (±39)		359 (±50)			374 (±77)
AoV	$F = 1.31$, $p = 0.260$		$F = 2.13$ $p = 0.050$		$F = 2.16$, $p = 0.046$		$p \geq 0.05$	
t	11–15/91–95 = 0.29		91–95/181–186 = 1.15		181–186/11–15 = 1.41		[b] $p = 0.03$	
AoV	all devices, all sequences, $F = 2.07$, $p = 0.130$							

Air flow rate 60 l min^{-1} through device; lot K, 5 shots per device.
[a] $n = 4$, analytical sample lost.

Table 4
Fine particle dose (0.5–6.4 μm MMAD) delivered from Bricanyl Turbohalers™

Turbohaler lot E					Turbohaler lot K			
TBH code	Shot no.	Fine particle dose (μg)		't' 11–15/16–20	TBH code	Shot no.	Fine particle dose (μg)	
		Mean (±SD)	Range				Mean (±SD)	Range
E1	11–20	264 (±64)	183–370	0.95	K1	1–15	240 (±58)	154–337
E2	11–20	287 (±33)	242–358	0.24	K2	1–15	215 (±49)	119–228
E3	11–20	329 (±34)	277–385	0.40	K48	1–5	99 (±37)	59–157
E4	11–20	265 (±50)	192–378	0.12	K49	1–5	221 (±35)	176–267
E5	11–20	204 (±58)	123–275	0.76	K50	1–5	223 (±39)	177–282
E6	11–20	221 (±73)	85–308	0.14	K51	1–5	232 (±52)	166–284
E7	11–20	207 (±39)	142–255	1.17	K52	1–5	198 (±45)	159–251
E8	11–20	260 (±60)	159–335	2.37 [a]	K53	1–5	167 (±25)	127–188
E9	11–20	187 (±40)	127–257	1.61	K54	1–5	238 (±33)	203–292
E10	11–20	262 (±40)	203–324	1.89	K55	1–5	216 (±19)	191–245
E11	11–20	247 (±51)	159–340	0.80	K56	1–5	232 (±13)	221–253
					K57	1–5	201 (±29)	172–246
					K58	1–5	204 (±46)	150–249
					K59	1–5	191 (±16)	174–210
All shots	11–15	245 (±60)		0.52	all shots	1–5	(208±52)	
[a] $p = 0.045$	16–20	252 (±65)			all shots (excl. K48)	1–5	(216±43)	
Mean values								
Device mean		249 (±41)			device mean		206 (±37)	
(Excl. E3)		241 (±33)			device mean (excl. K48)		214 (±21)	
All shots ($n = 110$)		249 (±62)			device mean for K60–K74		209 (±30)	
(Excl. E3 ($n = 100$)		241 (±56)			(3 shots per device)			
All 't'-tests show differences between lots					all K1, K2, K48–K59 ($n = 90$)		210 (±51)	
E and K are significant ($p < 0.05$)					all K1, K2, K48–K74 ($n = 135$)		210 (±48)	
					excl. K48,	($n = 85$)	217 (±44)	
						($n = 130$)	214 (±44)	
Analysis of variance								
E1–E11,		$F = 6.84$, $p \rightarrow$ zero			K1, K2, K48–K59,		$F = 4.11$, $p \rightarrow$ zero	
Excl. E3,		$F = 4.20$, $p \rightarrow$ zero			excl. K48,		$F = 1.43$, $p = 0.17$	

Air flow rate 60 l min^{-1} through devices.

significantly lower than the mean of 385 ± 31 μg (range 319–456 μg) for the 59 devices assessed at 60 l min^{-1} ($t = 2.69$, $p < 0.01$). Consequently, studies were extended to determine single shot drug emission using the TSI set to draw 30 l min^{-1} through the device. Shots 1–5 were sampled from each of five further devices giving mean emitted dose values of 325 ± 71, 353 ± 133, 310 ± 134, 180 ± 51 and 163 ± 62 μg. Three of these devices gave values within the Andersen range, but two delivered only half as much. It is also clear that the variability of delivery per single shot is much increased, coefficients of variation per device ranging from 22 to 43% compared to 9–26% for the corresponding shot numbers from devices sampled at 60 l min^{-1}.

3.3. Fine particle dose and fraction

This is the fraction of the aerosolised cloud potentially capable of deposition in the lower airways and was determined at flow rates of 60 l min^{-1} (TSI, 0.5–6.4 μm) and 28.3 l min^{-1} (Andersen 0.4–5.8 μm). The TSI data for single doses are shown in Tables 4 (dose) and 5 (fraction), respectively. The grand mean fine particle dose per device for the 25 Turbohalers™ examined was 224 ± 44 μg, individual shot values rang-

Table 5
Fine particle fraction (0.5–6.4 μm MMAD) delivered from Bricanyl Turbohalers™

Turbohaler lot E					Turbohaler lot K			
TBH code	Shot no.	Fine particle fraction (%)		't' 11–15/16–20	TBH code	Shot no.	Fine particle fraction (%)	
		Mean (±SD)	Range				Mean (±SD)	Range
E1	11–20	63 (±13)	39–78	2.70 [a]	K1	1–15	60 (±10)	39–79
E2	11–20	67 (±4)	61–73	1.30	K2	1–15	53 (±10)	32–66
E3	11–20	70 (±5)	59–74	0.64	K48	1–5	25 (±5)	18–38
E4	11–20	66 (±5)	59–75	0.40	K49	1–5	51 (±6)	44–56
E5	11–20	51 (±8)	40–59	0.79	K50	1–5	58 (±10)	48–70
E6	11–20	59 (±14)	22–72	0.40	K51	1–5	60 (±6)	53–69
E7	11–20	48 (±7)	38–61	0.34	K52	1–5	50 (±7)	42–60
E8	11–20	58 (±7)	44–68	0.71	K53	1–5	45 (±4)	39–49
E9	11–20	52 (±8)	37–61	0.59	K54	1–5	55 (±6)	48–64
E10	11–20	59 (±7)	51–72	zero	K55	1–5	60 (±5)	53–66
E11	11–20	57 (±7)	46–70	0.77	K56	1–5	59 (±2)	57–61
					K57	1–5	54 (±4)	49–59
				[a] $p = 0.027$	K58	1–5	55 (±3)	51–60
					K59	1–5	57 (±3)	52–61
All shots	11–15	58.8 (±10.4)		0.26	all shots	1–5	53.7 (±11.3)	
	16–20	59.3 (±10.1)			all shots (excl. K48)	1–5	55.9 (±7.9)	
Mean values								
Device mean		59.0 (±6.9)			device mean		53.1 (±9.2)	
All shots ($n = 110$)		59.0 (±10.2)			device mean (excl. K48)		55.2 (±4.6)	
t-tests for lot nos E and K show:					device mean for K55–K69 (3 shots per device)		55.3 (±5.4)	
Device means not significantly different, $p > 0.05$					all shots K1, K2, K48–K59 ($n = 90$)		53.8 (±10.7)	
All shot means are significantly different, $p < 0.01$					all shots K1, K2, K48–K74 ($n = 135$)		54.3 (±9.3)	
					excl. K48, ($n = 85$)		55.5 (±8.1)	
					($n = 130$)		55.5 (±7.3)	
Analysis of variance								
E1–E11,		$F = 9.40$, $p \rightarrow$ zero			K1, K2, K48–K59,		$F = 8.15$, $p \rightarrow$ zero	
Excl. E3		$F = 7.54$, $p \rightarrow$ zero			excl. K48,		$F = 2.22$, $p = 0.019$	

Air flow rate 60 l min^{-1} through devices.

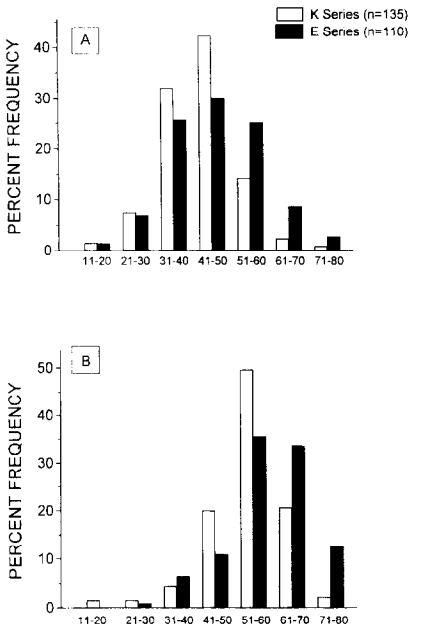

Fig. 3. Frequency distribution for fine particle drug fraction delivered from Bricanyl Turbohalers™ (air flow rate: 60 l min^{-1}). (A) As percent nominal dose; (B) as percent emitted dose. Ordinate, percent frequency; abscissa, dose interval (μg).

ing from 59 to 385 μg. Analysis of variance (Table 4) showed inter-device performance was significantly different for both Turbohaler™ batches examined. For lot K this was entirely associated with device K48 which gave an abnormally low mean fine particle dose (99 μg) although its mean emitted dose (395 μg) was not. Batch comparison was carried out both on the basis of mean per device and individual shot values including and excluding K48 and E3 (significantly different from other E devices). Additional data were also available for devices K60–K74 and this too was incorporated into the analysis. In every comparison mode, 't' values were significant ($p < 0.05$), thus lot E gave the better performance which is also apparant from the frequency distribution plots of fine particle dose as percent nominal and percent emitted dose (Fig. 3). The fine particle doses of 249 ± 62 μg (lot E, $n = 110$) and 210 ± 48 μg (lot K, $n = 135$), are both closer to that of 250 μg (replicates unspecified) reported by the Turbohaler designers (Jaegfeldt et al., 1987) than the data derived from cumulative shot collection by Bell (1992), 121 ± 39 μg ($n = 30$) and Newman et al. (1989), 178 ± 31 μg ($n = 5$). Their results do, however, fall within the range shown in Table 4, although Newman et al. (1989) have again normalised against a 500 μg emitted dose and their value is therefore questionable.

Whilst the fine particle dose of drug is the clinically important parameter, it is a composite function of the efficiency of dose metering, drug deposition within the device and particle de-aggregation. Normalisation of data by calculating fine particle fraction as a percent of emitted dose deletes the dose metering and device deposition factors and allows comparison of de-aggregation performance. Analysis of variance (Table 5) again shows there is significant inter-device variation within each batch. Mean fine particle fraction for lot E was 59% compared to 55% for lot K (excluding the value of 25% for K48). Inter batch comparison showed these values were statistically significant ($p < 0.01$) when examined on an individual shot basis but not for device mean values (Table 5). This finding has potential implications for the manner in which fine particle fraction data should be determined and presented, i.e., single shot or cumulative shots.

Reducing the air flow rate through the device to 28.3 l min^{-1} can be expected to reduce the particle-particle disruption forces within the device and so reduce fine particle dose and fraction. A cumulative five-shot sequence obtained by Andersen sampling of the particle cloud from each of 10 devices from lot K gave a mean fine particle dose of 59 ± 25 μg which is less than one third of the value (210 μg) obtained at 60 l min^{-1}. The MMAD of each particle cloud was determined from log/probit transformation of the particle size/percent fraction undersize data since this gave better linearity ($r \geq 0.910$) than conventional log-probability plots. MMADs were consistent for the 10 devices ranging from 3.9 to 4.6 μm (mean value 4.5 ± 0.2 μm); apparent GSD values of 1.6–1.9 were estimated from $(84\%/16\%)^{0.5}$ particle size ratios but should be viewed with caution because of the data treatment method. For comparison, two devices from lot E were also sam-

pled giving MMADs of 4.2 and 4.7 μm, respectively.

The mean fine particle fraction for lot K derived from the Andersen data was 17% (±6) compared to 55% (±7) obtained at 60 l min^{-1}. The marked reduction in particle de-aggregation seen with the low flow rate multi-stage analyses is also supported by the TSI studies at 30 l min^{-1}. Although currently, experimental validation of the stage 1 cut-off at different flow rates is not in the literature, it can be estimated as 9.0 μm at 30 l min^{-1} from impactor theory (Hallworth and Westmoreland, 1987); thus, stage 2 deposition should increase and become similar to deposition on Andersen stages 0–7 (0.4–9.0 μm). The stage 2 fractions for the five devices under these conditions were 36% (±13), 23% (±9), 31% (±16), 10% (±7) and 5% (±3). The first four DPIs gave typical fine particle fractions at 60 l min^{-1} but the fifth device was abnormal (23%) as was a second device used in a latter part of the programme. A check on the desiccant capacity after breaking the device down revealed no obvious defect in this respect. Ignoring the rogue device, the average fine particle fraction per device (n = 4) was 25% ± 11 which is not significantly different from the equivalent Andersen data for stages 0–7 (0.4–9.0 μm) of 22% (±6), $t = 0.78$). More importantly, the single shot TSI data demonstrate the high variability of the de-aggregation process at flow rates of approx. 30 l min^{-1}.

Whilst our results for fine particle dose at 60 l min^{-1} are reasonably in line with those given by the device designers, the lower flow rate Andersen sampler data are not. Jaegfeldt et al. (1987) quote a fine particle dose value of 120 μg and a 100 μg value is to be inferred from the report of Wetterlin (1988). Our mean value of 59 μg is about half of these and additionally performance appeared to be much more erratic with individual determinations ranging from 24 to 103 μg (Fig. 4). A similar situation was seen with the very fine particle fraction (0.8–3.3 μm, stages 4–7) for which our mean value of 19 μg is one quarter of the 74 μg quoted by Jaegfeldt et al. (1987) who collected the emission from an inverted device. However, a control experiment showed drug emission and deposition was unaffected by device orientation when fired at this flow rate.

The apparent discrepancy between our Andersen data and those of Wetterlin (1988) is explainable in terms of data presentation, since his fine

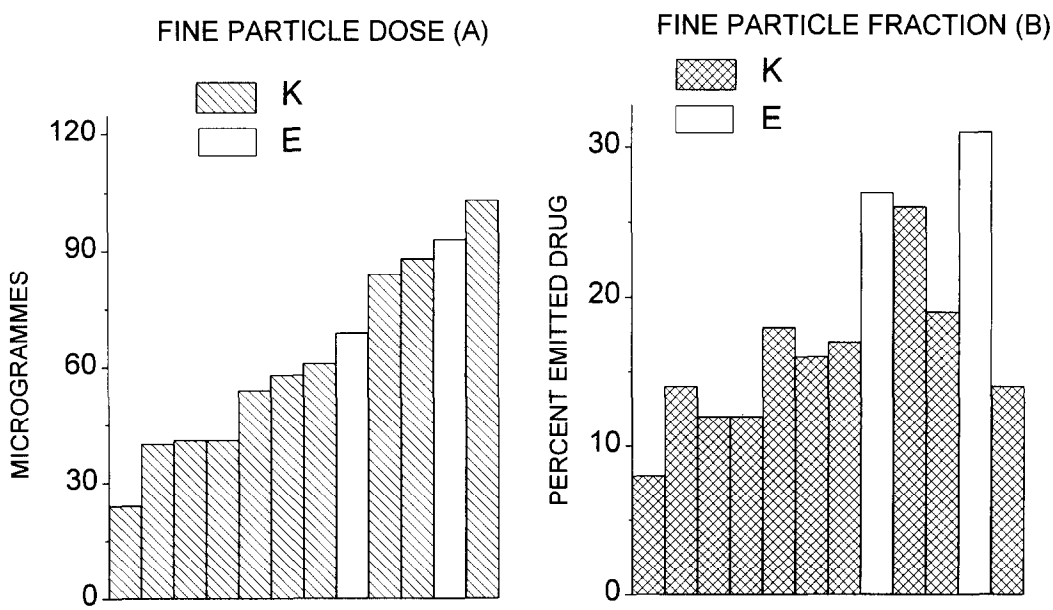

Fig. 4. Mean fine particle dose and fraction obtained from Bricanyl Turbohalers™ at 28.3 l min^{-1} flow rate. Ordinate: (A) μg; (B) % emitted drug.

particle 'dose' values are stated not as μg drug but as μg per mg. Thus, a normalisation process equivalent to that used by Newman et al. (1989) and analogous to our calculation of fine particle fraction has been used; (fine particle fraction × 10 ≡ μg per mg). Wetterlin's quoted values for four batches equate to respirable fractions at 28.3 l min^{-1} of 19% (±2), 21% (±4), 20% (±1) and 21% (±6) for three collection sequences from each of 10 devices per batch; the standard deviations given here have been calculated assuming the quoted standard errors relate to the 10 device means per batch rather than the 30 individual determinations. The 17% (±6) fine particle fraction found in this study is therefore very comparable and indeed is not significantly different ($t \leq 1.75$).

Another factor possibly contributing to differences in reported Turbohaler™ delivery characteristics is ambient humidity at the time of sampling (Plomp et al., 1987). Ambient temperature and relative humidity were monitored routinely over the 10 month study period ranging from 11 to 26°C and 43 to 72% RH. To permit comparison these were translated to absolute humidity, but there was no correlation with fine particle fraction for either TSI ($r = -0.045$, $p > 0.1$) or Andersen Sampler data ($r = 0.018$, $p > 0.1$). Any potential sampling air humidity effects are therefore completely obscured by inter-device variation. These findings are confirmed by the data of Lindberg (1993) showing no sampling humidity effects between 30 and 75% RH for Bricanyl Turbohalers™.

3.4. General conclusions

Clinical usage involves single doses, although data on the in vitro delivery performance of inhalation devices are normally presented on the basis of cumulative shot analysis which will reduce the apparent variability of drug delivery, in this study by a factor of approximately two. Currently the BP 1993 and USP XXII have only addressed the DPI single dose issue with respect to uniformity of weight and drug content of single dose capsule and blister units prior to dose emission and such standards are inappropriate for reservoir devices. Relevant to all DPI types, however, is a specification for dose emission and aerosol cloud quality based on single shot performance. In this context the drug delivery efficacy of terbutaline sulphate from Turbohaler™ has been evaluated, providing information on what is achievable by the one multi-dose reservoir DPI widely licensed in Europe. At 60 l min^{-1}, average drug dose emission is about 400 μg (80% nominal) with a likely range of approx. ±50% (±3SD). Fine particle fraction of the emitted dose is about 55–60% leading to a fine particle average dose of about 230 μg with a likely range of ±70%. However, it is important to stress this 'ex-device' delivery performance should not, mistakenly, be judged against standards set for capsule fill. Equally comparisons at a single impactor flow rate may also be misleading.

Aerosolisation and particle aggregate disruption are dependent upon intra and inter-particle forces within a given powder formulation and the disruptive stresses induced by the turbulent air stream on the fluidised aggregates. For a given device geometry, the disruptive stresses will be determined by air flow rate through the device and comparison in vitro studies should therefore take into account patients' lung function capability in this respect. Several recent studies (Sumby et al., 1992; Clark and Hollingworth, 1993; Richards and Saunders, 1993; Peart et al., 1994) have examined flow rate-pressure drop (resistance, R_D) relationships for currently licensed DPI systems including Turbohaler™, $R_D = 63$ $Pa^{0.5}$ s dm^{-3} which can be classified as a device of intermediate resistance (R_D range 42–67 $Pa^{0.5}$ s dm^{-3}; Byron et al., 1994). The results have been considered in terms such as 'required inspiratory effort', and level of patient comfort and acceptability. However, these authors have not compared DPI drug delivery characteristics under 'equivalent effort' flow rates presumably due to the fact the currently recognised impactor devices are calibrated at either 28.3 or 60 l min^{-1}, which flow rates are clearly relevant to Turbohaler but not necessarily for other DPI systems. Thus, simplistic comparison between DPI systems using a given test procedure should be viewed with considerable caution even when the identical drug

substance is involved. There is clearly a need for DPI performance to be assessed under conditions which are consistent at least with average through-device flow rates achievable by patients. The discrepancies between nominal dose and actual emission described here also sustain the proposals of the USP Advisory Panel on Aerosols (Byron et al., 1994) to label DPI systems with the emitted dose at this relevant flow rate.

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