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International Journal of Pharmaceutics 154 (1997) 19–29

international journal of pharmaceutics

In vitro evaluation of dry powder inhalers I: drug deposition of commonly used devices

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Received 16 December 1996; received in revised form 25 March 1997; accepted 4 April 1997

Abstract

Inhalation of aerosolized drugs has become the therapy of choice for the treatment of lung diseases. The most commonly used device, the pressurized metered-dose inhaler (pMDI), however, relied on propellants that were found to deplete the ozone layer. To overcome this drawback dry powder inhalers (DPI) have been developed and MDIs with alternative propellants have been introduced recently. Several products are available by now. This study was carried out to evaluate the accuracy of the dose and the theoretically respirable fraction emitted from commonly used DPIs. In vitro measurements were performed using the Twin Impinger (Appendix A, British Pharmacopoiea, 1993) and a self constructed Four Stage Impinger at the standard flow rate of 60 l min^{-1}. Eleven dry powder formulations that are commercially available on the german market were tested with eight dry powder devices: Pulmicort™ and Aerodur™ Turbuhaler™, Intal™ Spinhaler™, Flui™ SCG and Cromolyn™ Orion Inhaler, Sultanol™ Diskhaler™, Flutide™ Diskus™, Atrovent™ with Inhalator M™, Ventilat™ with Inhalator Ingelheim and Buventol™ and Beclomet™ Easyhaler™. As every dry powder inhaler has a specific air flow resistance that limits flow under in vivo conditions, inhaler devices should be tested at corresponding flow conditions in vitro. Though this is not yet reflected in the pharmacopeias, a general consensus can be seen in the scientific literature. Therefore DPIs having a high resistance were tested at 30 l min^{-1} and those showing a low resistance at 90 l min^{-1} with the Twin Impinger additionally. Most products were found to emit a fine particle dose of 20–30% of total emitted dose at 60 l min^{-1}. The results of the Twin Impinger and the Four Stage Impinger were in good agreement. Measurements at increasing flow rates generally resulted in increasing fine particle fractions. © 1997 Elsevier Science B.V.

Keywords: Dry powder inhaler; Multi stage liquid impinger; Twin impinger; Respirable fraction; Dose emission; Device resistance

1. Introduction

Dry powder inhalers (DPIs) are well established for delivery of aerosols to the respiratory tract in

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PII S0378-5173(97)00113-0

the treatment of lung diseases (Timsina et al., 1994). They allow the generation of aerosols without the use of propellants and the efficiency of inhalation is independent of the coordination of inhalation and actuation as opposed to metered-dose inhalers (Crompton, 1982). A variety of dry powder delivery systems that are easy to operate and relatively inexpensive have been developed by now (Bell et al., 1971; Wetterlin, 1988; Sumby et al., 1993; Timsina et al., 1994; Brindley et al., 1995; Vidgren, 1995). Similar to metered-dose inhalers (MDIs) the fine particle fraction, comprising particles smaller than about 5 μm (Moren, 1992) is highly dependent on the formulation and the design of the dry powder inhaler (Hickey et al., 1994). A large number of factors have influence on the aerosolization of the powder within the device and the behaviour of the particles during the inhalation process: the method of drug micronization (jet milled drugs tend to be very cohesive), interparticulate forces (cohesion caused by van-der-Waals and electrostatic forces) and particle-surface interactions such as adhesion of drug onto the capsule or mouthpiece surface (Staniforth et al., 1981, 1982; Visser, 1989; Hickey et al., 1994). Furthermore, the design of the inhaler and its air flow resistance have great influence on the respirable fraction and its in vitro measurement (Moren, 1992).

The purpose of this study was to determine the fine particle fraction of commonly used dry powder inhalers. The results of two liquid impingers which both work at an air flow of 60 l min^{-1} were compared. Because of the very different resistance of inhalers the test conditions should be adapted. This is why devices with a high resistance (>0.12 (cm $H_2O)^{1/2}/l^{-1}$ min) such as Inhalator M™, Inhalator Ingelheim™ and the Easyhaler™ were tested at 30 l min^{-1} and those having a low resistance (<0.07 (cm $H_2O)^{1/2}/l^{-1}$ min) as for example the Spinhaler™, the Diskhaler™ and the ISF Inhaler™ (Clark and Hollingworth, 1993) at 90 l min^{-1} additionally. Because of the good agreement of the Twin Impinger and the Four Stage Impinger results the experiments at different air flow rates only were carried out with the Twin Impinger.

2. Materials and methods

2.1. Materials

The proprietary dry powder inhalers (including batch numbers) used in this study are listed in Table 1. Chemicals and solvents used were all HPLC grade and obtained from Merck, Darmstadt, Germany. Water was purified by double distillation.

2.2. HPLC assays

HPLC analysis was performed using a Gynkotek High Precision Pump, Model 300 (Gynkotek, Munich, Germany), a Kontron HPLC 360 Autosampler (Kontron Instruments, Milano, Italy), a Techlab SPD 6A UV detector and a Shimadzu C-R6 A Chromatopak integrator (Shimadzu, Kyoto, Japan). For all analytical procedures RP-18 LiChrospher 5 μm columns, 125 × 4.8 mm (Merck, Darmstadt, Germany) were used. The HPLC methods are summarized in Table 2. Drug amounts were determined by an external standard.

2.3. Particle size analysis

Two inertial devices were used for the determination of the fine particle fraction (particles <6.4 μm): the Twin Stage Impinger (TSI, Appendix A, British Pharmacopoiea, 1993) bought from Erweka Apparatebau (Heusenstamm, Germany) and a modified Multi Stage Liquid Impinger, MSLI (Fig. 1). This MSLI was used to obtain a better analysis of the particle size distribution as with the TSI that allows a separation into only two fractions, below and above 6.4 μm. The stage cut-off diameters ($D_{50\%}$) of the MSLI were calculated as 15.3, 6.4 and 1.0 μm at an air flow rate of 60 l min^{-1} following the equation

$$D_{50\%} = \sqrt{\frac{\mathrm{Stk}_{50} \cdot 9 \cdot \pi \cdot \eta \cdot W^3}{4 \cdot \rho_P \cdot Q \cdot C_c}}$$

where Stk_{50} is the Stokes Number (0.1160), η is the air viscosity (1.832×10^{-4} g cm^{-1} s^{-1} at 20°C and 1013 mbar), W is the jet diameter (mm), ρ_P is the particle density (1.0 g cm^{-3}), Q is the air

Table 1
Summary of dry powder inhalers tested in the study

Proprietary names	Trademark	Inhaler device	Active ingredient (mg)	Nominal dose (mg)	Carrier	Rechargeable	Batch number
Intal	Fisons (UK)	Spinhaler	Cromolyn sodium (SCG)	20	—	Yes	JE 5 E
Flui DNCG	Zambon (GER)	Flui Inhaler	Cromolyn sodium (SCG)	20	Lactose	Yes	52603
Cromolyn Orion	Orion (SF)	Orion Inhaler	Cromolyn sodium (SCG)	20	Lactose	Yes	TH 2
Aerodur	Astra (S)	Turbuhaler	Terbutaline sulphate (TBS)	0.5	—	No	TB 393
Sultanol	Glaxo (UK)	Diskhaler	Salbutamol sulphate (SBS)	0.2	Lactose	Yes	2K 154183
Buventol	Orion(SF)	Easyhaler	Salbutamol sulphate (SBS)	0.1	Lactose	No	TL 5-1
Pulmicort	Astra (S)	Turbuhaler	Budesonide	0.2	—	No	VA 638
Flutide	Glaxo (UK)	Diskus	Fluticasone-17-propionate	0.1	Lactose	No	WO 66
Beclomet	Orion (SF)	Easyhaler	Beclometasone-dipropionate (BMDP)	0.2	Lactose	No	VM 33-1
Atrovent	Boehringer (GER)	Inhalator M	Ipratropium bromide	0.2	Glucose	Yes	52120
Ventilat	Thomae (GER)	Inhalator Ingelheim	Oxitropium bromide	0.1	Glucose	Yes	22464

Table 2
Analytical assays of the HPLC analysis

	Mobile phase	Flow rate (ml/min)	Pressure (MPa)	Retention time (min)	Wavelength (nm)
Salbutamole sulphate	54% H_2O, 44% MeOH	1.2	15.0	3.1	280
Terbutaline sulphate	+1,1 g Na Heptanesulfonic acid	1.2	15.0	3.2	280
Sodium cromoglycate	55% MeOH, 45% H_2O+7 g Tetrabutylammoniume sulfate	1.2	16.5	3.5	238
Budesonide	45% Acetonitrile, 55% H_2O	1.2	9.0	3.9	254
Beclomethasone	60% Acetonitrile, 40% H_2O	1.2	7.8	3.5	237
Flunisolide	35% Acetonitrile, 65% H_2O	1.2	9.5	4.1	237
Fluticasone	60% Acetonitrile, 40% H_2O	1.2	7.8	3.5	237
Ipratropiumbromide	Tetrahydrofurane, MeOH, H_2O (5:13:82)	2.0	22.0	9.0	210
Oxitropiumbromide	+Na-Heptanesulfonic acid	2.0	22.0	7.0	210

flow (60 l min^{-1}) and C_c is the Cunningham slip correction factor, which is dependent on the particle size, but is nearly one for particles less than 1 μm (Hinds, 1982; Hallworth and Westmoreland, 1987; Marple and Willeke, 1976; Marple, 1978).

Previous studies (Holzner and Müller, 1995; Holzner, 1995) have shown that the fractions below and above 6.4 μm in the TSI and the MSLI were identical. The MSLI, however, allows for a better analysis of the particle size distribution than the TSI, as it divides aerosol particles into four defined fractions, compared to the TSI's mere two. According to Gebhardt et al., 1978 who found that particles less than 1 μm will be exhaled the MSLI allows the determination of the effective dose (stage 3 of the MSLI with particles from 1.0 to 6.4 μm) of an aerosol. The equation above shows the dependence of the cut-off diameter on the adjusted air flow. As proposed by Moren (1992), dry powder inhalers should be tested at an appropriate flow with regard to their air flow resistance. Hence, 30 and 90 l min^{-1} were used additionally. The resulting cut-off diameters for the Twin Impinger are 9.08 μm at 30 l min^{-1}, 6.42 μm at 60 l min^{-1} and 5.24 μm at 90 l min^{-1} calculated from the equation above (Hallworth and Westmoreland, 1987).

2.4. Determination of in vitro drug deposition

The dry powder inhalers were attached to the inlet port of the impinger with a rubber gasket. Ten doses from each inhaler were released into the impinger, with exception of the SCG-products containing 20 mg SCG/dose where only one dose was used. The vacuum pump was turned on for 4 s to simulate an inhalation of 4 l (air flow: 60 l min^{-1}). This procedure was repeated as declared in the user instructions of each inhaler. All parts of the impinger were rinsed with water or with water/methanol-mixtures and adjusted to a known volume. The amount of drug in each stage was measured using the HPLC method described above (Table 2). The total amount of drug recovered in the impinger and the mouthpiece represents the emitted dose, drug recovery ex-device is equal to the delivered dose and particles smaller than 6.4 μm (stages 3 and 4) represent the fine particle fraction calculated as percentage of the total amount of drug recovered.

3. Results and discussion

The purpose of the study was to determine the respirable fractions (percentage of aerosolized

drug < 6.4 μm) of commonly used dry powder inhalers. Additionally, the delivered dose was calculated as total amount of drug released into the impinger. Two different impinger devices that both work at an air flow rate of 60 l min^{-1} were used. The dry powder inhalers differed in design, rechargability and the use of carrier excipients.

3.1. Fine particle fractions at 60 l min^{-1}

3.1.1. DPIs containing sodium cromoglycate

The same inhaler (ISF-Inhaler) is used for powder aerosolization of Flui™ SCG and Cromolyn™ Orion. For both formulations a fine particle fraction of roughly 30% of the drug was found. For the Spinhaler™ (Intal™) the fine particle fraction was 10% as determined with the TSI and 4% determined with the MSLI (Fig. 2 and Table 3). Due to the high content of drug in the Intal™ capsules (20 mg/capsule) 2 (TSI) and 0.8 mg, respectively (MSLI) were found to be in the respirable range, however. Thus the dose reaching the lung region is in the therapeutically sufficient range of 1 mg SCG (Mutschler, 1996).

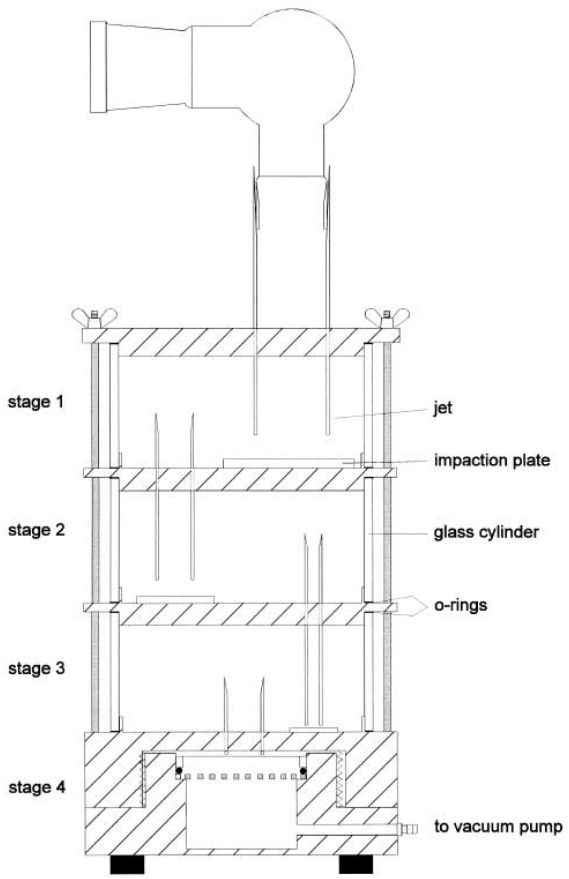

Fig. 1. The Four Stage Impinger.

3.1.2. DPIs containing β-adrenergic drugs

The following devices were investigated: Aerodur™ Turbuhaler™, Sultanol™ Diskhaler™ and Buventol™ Easyhaler™. All these powder inhalers were found to generate an aerosol cloud with more than 30% of particles below a particle size of 6.4 μm. This theoretical respirable amount is comparable with a good metered-dose inhaler (Holzner, 1995). Furthermore, the Easyhaler™ represents a device of simple construction and is very easy to use.

3.1.3. DPIs containing glucocorticoids

Pulmicort™ Turbuhaler™, Flutide™ Diskus™ and Beclomet™ Easyhaler™ showed differences in their fine particle fractions: the Diskus™ device was found to generate a powder aerosol of about 30% in the respirable range, the Beclomet™ Easyhaler™ about 20% and the Pulmicort™ Turbuhaler™ about nearly 40% as measured with both impingers.

3.1.4. DPIs containing cholinergic drugs

Atrovent™ aerosolized using Inhalator M™ and Ventilat™ aerosolized with the Inhalator Ingelheim™ had very similar particle size distributions and fine particle fractions of about 30%. This could be expected as both inhalers are very similar and differ only in size and the storage mechanism.

3.2. Fine particle fraction at different flow rates

Spinhaler™, Diskhaler™ and ISF-Inhaler™ are inhaler devices with a very low flow resistance and were therefore tested at 90 l min^{-1} additionally. The Inhalator M™, Inhalator Ingelheim™ and the Easyhaler™ were found to have a high flow resistance and were additionally measured at an air flow rate of 30 l min^{-1}. Turbuhaler™ and

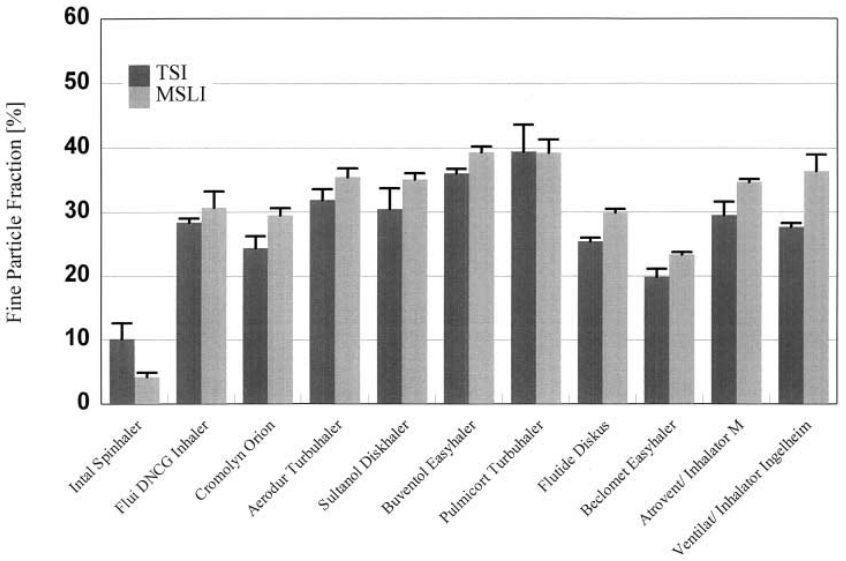

Fig. 2. Comparison of fine particle fractions measured with the Twin Impinger and the Four Stage Impinger.

Diskus™ are both medium resistance inhalers and were not tested at different flow rates as this was the subject of several earlier studies (Jaegfeldt et al., 1987; Fuller, 1995; Malton et al., 1995). The in-vitro deposition of these DPIs for both the pharmacopeial standard flow rate of 60 l min^{-1} and the flow rate adjusted to the powder device resistance is presented in Table 4. The measurements at the higher flow rate led to different results: Spinhaler™ and ISF-Inhaler™ emitted significantly ($P = 0.01$) higher fine particle fractions (lower impingement: < 5.24 μm) whereas deposition for the Diskhaler™ remained unaltered (Fig. 3). The reason for this observation might be seen in the mechanism of powder dispersion. Spinhaler™ and ISF-Inhaler™ are single unit dose inhalers where the drug is contained in gelatin capsules. These are rotated (Spinhaler™) or vibrated (ISF-Inhaler™) by the air stream. This movement facilitates powder dispersion and is the more intensive the higher the air flow is. As a side effect of the increased air flow a higher amount of drug remains within the mouthpiece as it impacts on the device walls. Powder dispersion in the Diskhaler™ is less dependent on the air flow because the powder in the pierced blister is more accessible.

Table 3
Fine particle fractions (%) of dry powder inhalers determined by using the Twin Impinger and a Four Stage Impinger at 60 l/min

Proprietary names	Drug <6.4 μm[a] (%)	
	Twin impinger	Four stage impinger
Intal Spinhaler	10.13 (2.51)	4.20 (0.69)
Flui SCG Inhaler	28.38 (0.64)	30.69 (2.56)
Cromolyn Orion Inhaler	24.35 (1.89)	29.48 (1.13)
Aerodur Turbuhaler	31.88 (1.67)	35.44 (1.38)
SultanolDiskhaler	30.45 (3.25)	35.08 (0.97)
Buventol Easyhaler	36.04 (0.70)	39.30 (0.91)
Pulmicort Turbuhaler	24.64 (1.79)	39.25 (2.03)
Flutide Diskus	25.41 (0.58)	29.91 (0.62)
Beclomet Easyhaler	19.87 (1.24)	23.34 (0.61)
Atrovent Inhaletten	29.51 (2.11)	34.65 (0.49)
Ventilat	27.68 (2.58)	36.38 (0.60)

[a] Mean value (standard deviation), $n = 3$.

Table 4
Drug deposition of dry powder inhalers in the Twin Impinger using different air flow rates

Air flow rate (l/min)	Spinhaler		ISF-Inhaler		Diskhaler		Inhalator M		Inhalator Ingelheim		Easyhaler	
	60	90	60	90	60	90	30	60	30	60	30	60
Mouthpiece	1.87	23.54	8.22	11.18	13.30	12.91	38.75	21.35	26.32	15.24	17.12	19.87
	(0.40)	(1.06)	(1.48)	(1.14)	(3.66)	(1.59)	(0.73)	(1.41)	(2.15)	(0.94)	(2.65)	(0.16)
Upper impingement	85.94	53.78	67.43	58.44	56.25	54.96	35.51	49.14	46.77	57.08	50.22	44.09
	(2.91)	(2.92)	(0.42)	(0.80)	(0.41)	(0.92)	(0.19)	(0.69)	(2.46)	(1.54)	(1.71)	(0.55)
Lower impingement	11.90	22.68	24.35	30.38	30.45	32.13	25.74	29.51	26.91	27.68	32.66	36.04
	(2.51)	(2.51)	(1.89)	(1.94)	(3.25)	(2.52)	(0.65)	(2.11)	(0.31)	(0.60)	(0.94)	(0.70)

[a] Mean value (standard deviation), $n = 3$.

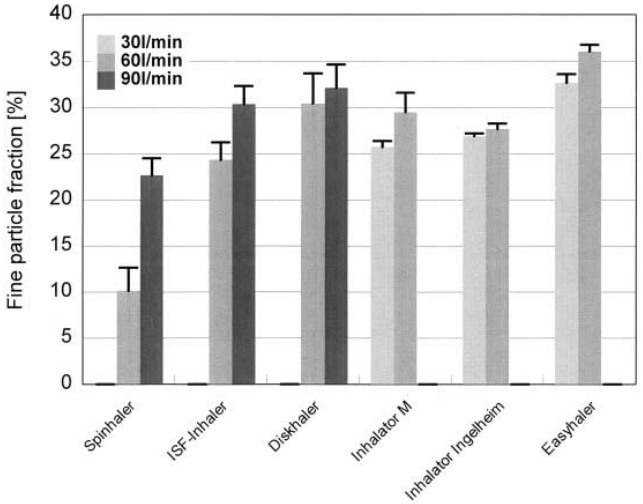

Fig. 3. Drug deposition in the lower impingement chamber of the Twin Impinger at different air flow rates.

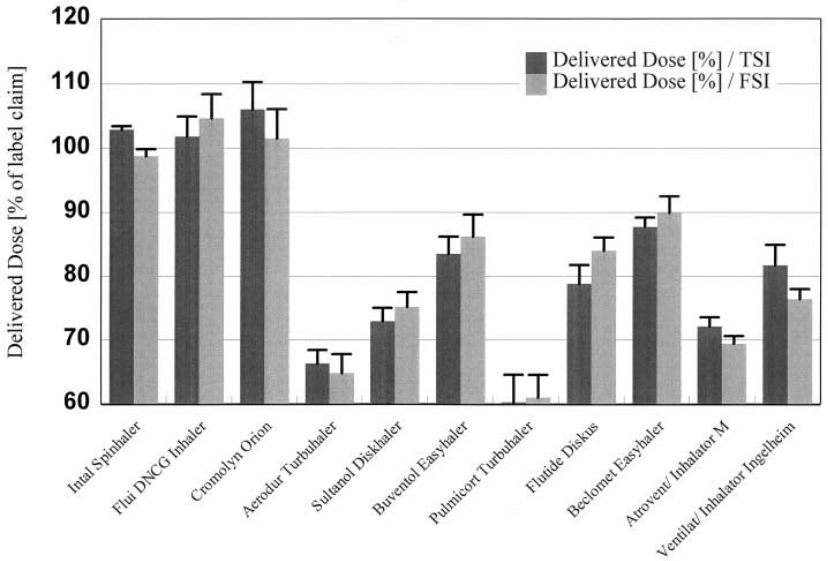

Fig. 4. Delivered dose of marketed dry powder inhalers.

The differences for fine particle fractions of the high resistance inhalers are less striking and only detectable if the higher cut-off diameter is taken into consideration when operating at a lower flow rate. Similar to the low resistance inhalers the fraction remaining within the mouthpiece is significantly higher ($P = 0.01$) for the capsule loaded Inhalator M™ and Inhalator Ingelheim™ (Table 4).

3.3. Dose accuracy

Fig. 4 shows the accuracy and reproducibility of the delivered dose from each of the 11 formulations. The delivered dose was calculated as the amount of drug leaving the inhaler expressed as percentage of the label claim. Device retention is shown in Fig. 5.

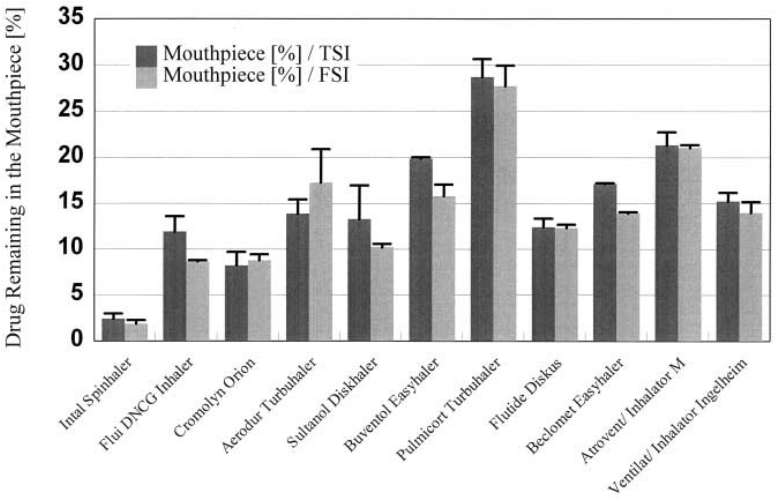

Fig. 5. Drug remaining in the mouthpiece of DPIs.

Obviously, all SCG inhalation capsules contained an overage of drug within the limits of the British Pharmacopoiea (1993) and delivered an average dose similar to the label claim. The delivered dose of all other devices investigated was significantly lower. It has to be kept in mind that emptying of the capsules usually is not complete. Consequently the metered dose is not equal to the delivered dose (Fig. 4). The fraction of drug remaining in the mouthpiece is generally in the range between 13 and 20% (Fig. 5 and Table 5), with the exception of Pulmicort™ Turbuhaler™ (28%) and all SCG-Inhalers ($< 10\%$). The data obtained with the TSI for both the delivered dose and the drug remaining in the mouthpiece correspond well with the MSLI data (Table 5).

All results are in good agreement with a study of Hindle and Byron (1995) who used a special sampling apparatus to determine the emitted dose. This suggests that the TSI could be used for determination of the emitted or the delivered dose as well.

Table 5
Delivered dose and percentage of drug remaining in the mouthpiece measured at 60 l/min

Proprietary names	Delivered dose[a] (% of label claim)		Drug remaining in the mouthpiece[a] (% of total amount recovered)	
	TSI	MLSI	TSI	MLSI
Intal Spinhaler	102.86 (0.55)	98.73 (1.10)	2.44 (0.55)	1.87 (0.41)
Flui SCG Inhaler	101.78 (3.10)	104.58 (3.75)	11.92 (1.67)	8.67 (0.20)
Cromolyn Orion Inhaler	105.95 (4.23)	101.45 (4.56)	8.22 (1.48)	8.78 (0.67)
Aerodur Turbuhaler	66.32 (2.08)	64.76 (3.01)	13.88 (1.55)	17.27 (3.65)
Sultanol Diskhaler	72.90 (2.12)	75.15 (2.35)	13.30 (3.66)	10.21 (0.36)
Buventol Easyhaler	83.57 (2.67)	86.19 (3.45)	19.87 (0.16)	15.80 (1.25)
Pulmicort Turbuhaler	60.25 (4.32)	60.95 (3.59)	28.74 (1.94)	27.74 (2.23)
Flutide Diskus	78.80 (2.97)	84.00 (2.05)	12.4 (0.94)	12.32 (0.36)
Beclomet Easyhaler	87.70 (1.47)	89.91 (2.57)	17.12 (0.15)	13.92 (0.13)
Atrovent Inhaletten	72.10 (1.46)	69.41 (1.20)	21.35 (1.41)	21.06 (0.31)
Ventilat	81.71 (3.21)	76.42 (1.57)	15.24 (0.94)	13.99 (1.18)

[a] Mean value (standard deviation), $n = 3$.

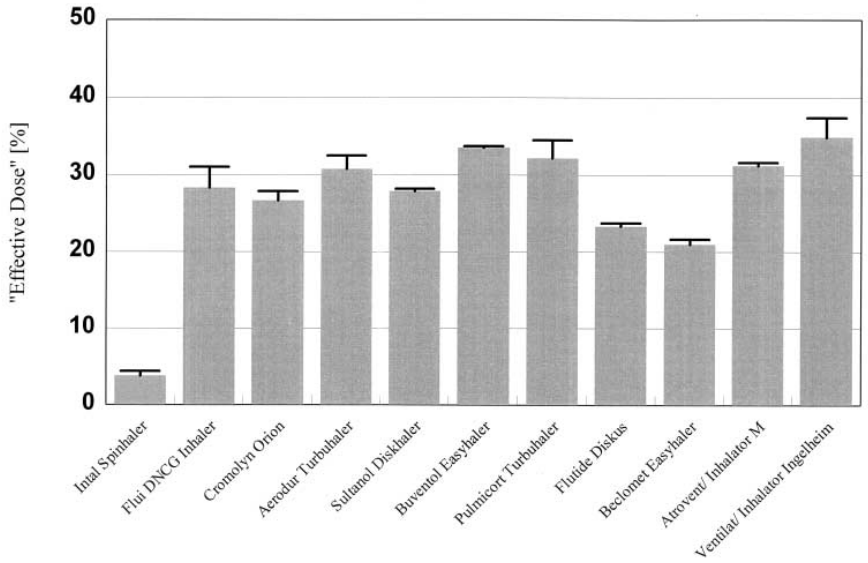

Fig. 6. Percentage of drug remaining in stage 3 of the Four Stage Impinger (1.0–6.4 μm).

3.4. Theoretical pulmonal dose

The third stage of the impinger was designed with regard to the fact that particles less than 1.0 μm do not impact or sediment within the lungs but will be exhaled. Keeping this in mind the percentage of drug recovered in stage 3 of the MSLI contains the particle fraction between 1 and 6.4 μm and is named 'effective dose'. Fig. 6 shows the effective dose of all devices investigated. Generally this was in the range of about 20–30% with the exception of the Intal™ Spinhaler™ (4%). The effective dose is in all cases lower than the total fine particle fraction with particles smaller than 6.4 μm (Figs. 2 and 6). The Easyhaler™ shows that the fine particle fraction as well as the effective dose are highly dependent on the powder formulation. A higher respirable fraction is achieved with salbutamol sulphate as with beclomethasone (35 vs. 21%). The latter observations were the basis for further experiments in another study with the Easyhaler™ and the Spinhaler™ varying the carrier particle size and the drug concentration.

4. Conclusions

All dry powder devices investigated deliver a drug dose of about 20–30% to the respiratory tract at a flow rate of 60 l min^{-1}. Where the SCG inhalers are concerned, it is however doubtful, if this high dose is necessary even if side effects are not to be expected. In the case of the Spinhaler™ the high amount of sodium cromoglycate serves as a carrier for itself and 85% of the drug remains in the upper stages of the impingers.

For the Flui™ SCG and the Cromolyn™ Orion Inhalers which achieve a suitable respirable fraction of about 30% (6–7 mg), the combination of 20 mg SCG with the carrier Lactose appears to be senseless from the therapeutical view as they deliver much more drug than therapeutically necessary (1–2 mg). All SCG products contain 20 mg of active drug but the dispersion with lactose as carrier seems to be more effective and has a positive influence on the dry powder dispersion compared to the dispersion of pure drug.

Obviously, the measured fine particle fraction from dry powder inhalers is in most cases higher

when a MSLI is used. This is in accordance to the work of Venthoye et al. (1995) who remarked similar effects by comparing the respirable fractions measured with the TSI, a MSLI and the Anderson Mark II impactor.

The findings at different flow rates enclose the necessity to test DPIs at flow rates depending on their resistance (Moren, 1992; Clark and Hollingworth, 1993) even if in-vivo studies showed no differences in the clinical effect if different inhalation flows were applied (e.g. Newman et al., 1991; Zanen et al., 1991).

References

Hindle, M., Byron, P.R., 1995. Dose emissions from marketed dry powder inhalers. Int. J. Pharm. 116, 169–177.

Bell, J.H., Hartley, P.S., Cox, J.S.G., 1971. Dry powder aerosols I: a new powder inhalation device. J. Pharm. Sci. 60, 1559–1564.

Brindley, A., Sumby, B.S., Smith, I.J., Prime, D., Haywood, P.A., Grant, A.C., 1995. Design, manufacture and dose consistency of the Serevent Diskus inhaler. Pharm. Tech. 1, 27–32.

British Pharmacopoiea, 1993. British Pharmacopoeial Comission, HMSO, London.

Clark, A.R., Hollingworth, A.M., 1993. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers-implications for in-vitro testing. J. Aerosol. Med. 6, 99–110.

Crompton, C.G., 1982. Problems patients have using pressurized aerosol inhalers. Eur. J. Respir. Dis. 63, 101–110.

Fuller, R., 1995. The Diskus: a new multidose powder device-efficacy and comparison with Turbuhaler. J. Aerosol Med. 8 (Suppl. 2), 11–17.

Gebhardt, J., Heyder, J., Stahlhofen, W., 1978. Deposition of aerosol particles in the human respiratory tract. Atemwegs- und Lungenkrankheiten 4, 384–389.

Hallworth, G.W., Westmoreland, D.G., 1987. The twin impinger: a simple device for assessing the delivery of drugs from metered-dose pressurized inhalers. J. Pharm. Pharmacol. 39, 966–972.

Hickey, A.J., Concessio, N.M., Van Oort, M.M., Platz, R.M., 1994. Factors influencing the dispersion of dry powders as aerosols. Pharm. Tech. 8, 58–64.

Hinds, W.C., 1982. Aerosol Technology: properties, behaviour and measurement of airborne particles. Wiley, New York.

Holzner, P.M., Müller, B.W., 1995. Particle size determination of metered dose inhalers with inertial separation methods: Apparatus A and B (BP), Four Stage Impinger and Anderson Mark II Cascade Impactor. Int. J. Pharm. 116, 11–18.

Holzner, P.M., 1995. Pharmazeutische Aerosole-Methoden zur Erzeugung, Charakterisierung und Bewertung, PhD thesis, Christian-Albrecht-University, Kiel.

Jaegfeldt, H., Andersson, J.A.R., Trofast, E., Wetterlin, K., 1987. Particle size distribution from different modifications of Turbuhaler. A new concept in inhalation therapy. Medicom, London, pp. 90–99.

Malton, A., Sumby, B.S., Smith, I.J., 1995. A comparison of in vitro drug delivery from two multidose powder inhalation devices. Eur. J. Clin. Res. 7, 177–193.

Marple, V.A., Willeke, K., 1976. Impactor design. Athmospheric Environ. 10, 891–896.

Marple, V.A., 1978. Simulation of respirable penetration characteristics by inertial impaction. J. Aerosol Sci. 9, 125–134.

Moren, F., 1992. Towards satisfactory in vitro testing requirements for single and multi-dose powder inhalers. J. Pharm. Sci. 3 (1/2), 123–129.

Mutschler, E., 1996. Therapie des Asthma Bronchiale. In: Mutschler, E. (Ed.), Arzneimittelwirkungen, wissenschaftliche Verlagsgesellschaft, Stuttgart.

Newman, S.P., Moren, F., Trofast, E., Talaee, N., Clarke, S.W., 1991. Terbutaline sulphate Turbuhaler: effect of inhaled flow rate on drug deposition and efficacy. Int. J. Pharm. 74, 209–213.

Staniforth, J.N., Rees, J.E., Lai, F.K., Hersey, J.A., 1981. Determination of interparticulate forces in ordered powder mixes. J. Pharm. Pharmacol. 33, 485–490.

Staniforth, J.N., Rees, J.E., Lai, F.K., Hersey, J.A., 1982. Interparticle forces in binary and ternary ordered powder mixes. J. Pharm. Pharmacol. 34, 141–145.

Sumby, B.S., Churcher, K.M., Smith, I.J., Grant, A.C., Truman, K.G., Marriott, R.J., Booth, S.J., 1993. Dose reliability of the Serevent Diskhaler system. Pharm. Tech. 6, 20–28.

Timsina, M.P., Martin, G.P., Marriott, C., Ganderton, D., Yianneskis, M., 1994. Drug delivery to the respiratory tract using dry powder inhalers. Int. J. Pharm. 101, 1–13.

Venthoye, G., Taylor, K.M.G., Newton, J.M., Johnson, M.C.R., 1995. The application of three different inertial impaction methods to study variations in samples of micronised and spray dried salbutamole sulphate. Drug Del. Lungs VI, 94–97.

Vidgren, M., 1995. Easyhaler multiple unit dose inhaler-practical and effective alternative to the pressurized MDI. Aerosol Sci. Technol. 22, 335–345.

Visser, J., 1989. Van der Waals and other cohesive forces affecting powder fluidization. Powder Technol. 58, 1–10.

Wetterlin, K., 1988. Turbuhaler: a new powder inhaler for administration of drugs to the airways. Pharm Res. 5, 506–508.

Zanen, P., vanSpiegel, P.I., van der Kolk, H., Tushuizen, E., Enthoven, R., 1991. The effect of the inhalation flow on the performance of a dry powder inhalation system. Int. J. Pharm. 81, 199–203.