Is inhalation rate important for a dry powder inhaler? using the In-Check Dial to identify these rates

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Abstract The fraction of the emitted dose from an inhaler that has the potential to be deposited into the lungs is known as the fine particle dose (also the respirable dose). During inhalation all dry powder inhalers require a 'force' to be created inside the device so that a fine particle dose is generated from the formulation in the metering chamber. This 'force' is formed by the inhalation rate used together with the resistance (and hence design) inside an inhaler. Studies have shown that the fine particle dose is related to the clinical effect whilst other studies have reported that this dose can be dependent on the inhalation rate used. The inhalation technique recommended by the manufacturer of an inhaled device should, therefore, be used. For those dry powder inhalers that demonstrate significant flow dependent dosage emission it is important that patients use the most desirable rate that has been reported. The In-Check Dial is a simple and ease to use meter that can be used to measure the inhalation rate of a patient when they use each of the commonly prescribed inhalers that are currently available. This meter can be used to identify the most suitable inhaler for each individual.

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Keywords dry powder inhaler; inhalation rates; in-check dial.

To ensure effective and consistent management of asthma or chronic obstructive pulmonary disease, it is essential that patients are compliant and that they can use their inhaled medication according to the instructions provided by the manufacturers. For the latter, it may be necessary to train the patient with the required inhalation technique for the inhaler they have been prescribed. However, studies have shown that although training enables the correct technique to be used these improvements for both metered dose inhalers (MDIs) (1,2) and dry powder inhalers (DPIs) (3) are only temporary.

Although the MDI is the most commonly prescribed device patients have problems with co-ordinating the start of inhalation with actuating a device (4,5). Co-ordination problems can be overcome by either attaching a spacer or a breath-actuated MDI. The inhalation used with a MDI should not be too fast otherwise central deposition in the large airways will predominate (6). All DPIs are breath actuated, but each type of device requires a different technique together with a disparate method of preparing a dose for inhalation.

There are many types of DPIs and each is designed to emit a consistent dose over a specific range of inhalation rates. To identify the patient's inhalation rate through an inhaler, and therefore the device to suit a patient's natural technique, the In-Check Dial (Clement Clarke International) has been introduced. Use of this device in the Clinic should enable the prescriber to choose an inhaled device that requires minimal training of the recommended inhalation technique.

Figure 1 shows that the In-Check Dial is similar in appearance to a peak flow meter. The difference is that inhalation is used rather than a forced expiration. The rate of inhalation is measured by reading the value on the meter (analogous to that of the measured peak flow). The In-Check Dial is designed to mimic the use of a specific inhaled device. Each setting on the dial corresponds to a different type of inhaler (e.g. Autohaler—3M Healthcare Ltd, Clickhaler—Medeva Pharma Ltd, Diskus, known in the U.K. as the Accuhaler—GlaxoSmithKilne, Easi-Breathe—Norton Healthcare, and Turbuhaler—Astra-Zeneca). When the patient inhales through the In-Check Dial, the reading provides the inhalation rate that would be obtained when using the inhaler for which the meter has been set for.

Respirable dose emitted from an inhaler

The recommended inhalation technique for each DPI device ensures that a dose of particles with the potential of

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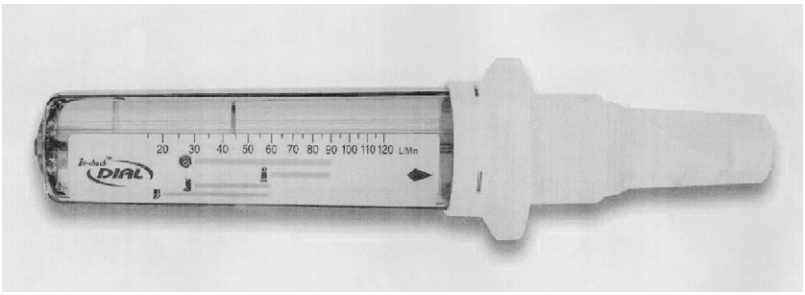

Fig 1. The In-Chek Dial.

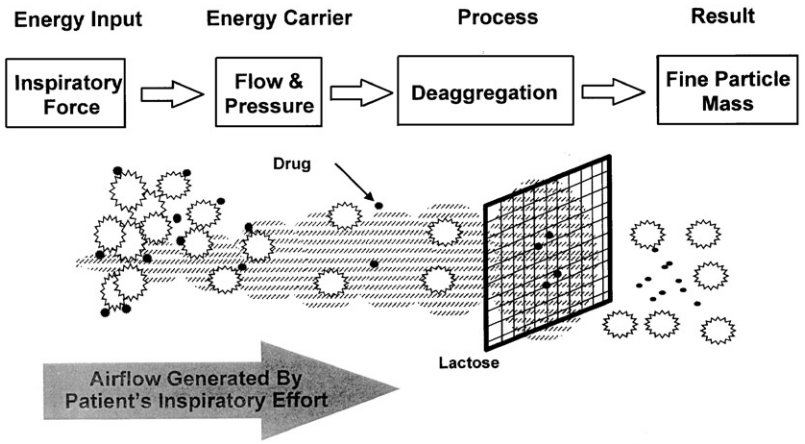

Fig. 2. The process of generating a respirable dose from a formulation of micronised drug and lactose in a DPI.

deposition into the airways is created during each inhalation. Particles between 1 and 5 μm have the greatest potential to deposit in the lungs, during an inhalation (7), with an even distribution throughout the airways (8). This fraction of the emitted dose from an inhaler is termed the respirable dose (also fine particle dose or respirable fraction).

During manufacture and dose metering it is essential that the powder has consistent, smooth flow. However, particles smaller than 5 μm do not have these flow properties and thus modifications to the formulation are required. Two different principles are used to improve flow. The most common is to mix the drug particles with an inert carrier whose particles are larger. The most common carrier is lactose. The two powders are mixed together and the adhesion of the drug to the carrier is such that there is no separation. During inhalation there has to be a break of this weak bond between the drug and its carrier to generate the respirable dose. This break is caused by the generation of 'force' within the device during inhalation. This 'force' is created from a patient's inhalation by resistance in the device as shown in Fig. 2. The other method used to improve flow is to formulate the drug into spheres (e.g. Turbuhaler). During inhalation 'force' is required to generate a respirable dose. Like the lactose formulations this 'force' is created from the patient's inhalation rate by resistance inside the device to ensure that turbulence of airflow is created to break up the spheres into particles of the required resprable size.

The design of each type of DPI is optimised to emit their formulation as a respirable dose during inhalation. Due to different formulations the resistance in each type of DPI is different. Inhalation rate is very important to generate the respirable dose from a DPI. All patients will inhale at a different rate and thus the design and formulation of each inhaler should be such that the most desirable range of inhalation rates required is achievable by all patients, of all ages and at all times.

Studies have shown that the dose emitted from some DPIs is dependent on flow (9–11). These are *in vitro* studies that also highlight that for some DPI devices there is a large variability in the emitted dose at a set inhalation rate. These *in vitro* properties of flow-dependent dose emission are, however, insignificant if they are not clinically relevant.

The respirable dose and clinical effect

Bronchodilators

It has been reported that the total dose deposited into the lungs is more important than regional distribution (8). An analysis of studies investigating lung deposition using gamma scintigraphy has shown that there is a significant correlation between the total lung dose and the fine particle dose (12). Similar relationships have been shown using urinary pharmacokinetic methods designed to identify total lung deposition (13,14). The clinical relevance of different lung deposition is difficult to apply to an inhaled bronchodilator drug. Urinary pharmacokinetic studies have shown that the Turbuhaler deposits twice as much drug into the lungs than the equivalent dose from a MDI (15). Spirometry in this study only revealed a difference for the lower dose inhaled from the MDI. This problem of doses at the top of the dose response curve is highlighted by a study, which showed that although lung deposition from an MDI and MDI attached to a spacer was 12.3 and 23.5%, respectively, there was no difference in spirometry (16). In another study, no difference in spirometry measurements were found following cumulative doses from a MDI and Turbuhaler (17). However, simultaneous measurement of heart rate did highlight the greater emitted dose from the Turbuhaler. Similar indirect indications of flow-dependent dose emission from a Turbuhaler were reported in a study by Engel *et al.* (18). Following inhalation of terbutaline from a Turbuhaler using rates of 34 and 84 l min^{-1}, the change in FEV_1 was 8 and 11.5%, respectively, whereas *in vitro* measurement of the emitted dose was much greater at the higher flow rate. This suggests that the spirometry measurements were at the top of the dose response relationship. The difference in the emitted dose was highlighted by significantly ($P < 0.01$) lower plasma terbutaline concentrations for the inhalation at 34 l min^{-1}.

The confusion from measurements at the top of dose response relationships with therapeutic doses of bronchodilators and thus the difficulty to demonstrate the clinical relevance of flow-dependent dose emission has been further demonstrated in children (19). Inhalations below 30 l min^{-1} demonstrated a dose response relationship, but there was no difference above 30 l min^{-1}. Although a much larger dose inhaled at each flow rate later in the study day did show equal (and greater) bronchodilation, this was given when the airways had been previously dilated 6 h earlier, and was also inhaled at a different time of the day. A link between better clinical response, inspiratory capacity and dose emission from the Turbuhaler was demonstrated by Hirsch *et al.* (20). They reported that the children with higher inspiratory capacity obtained an improved bronchodilatory effect. A further report, in abstract form, has also highlighted the relationship between inhalation rate through the Turbuhaler and response (21).

Corticosteroids

For corticosteroids, the measurement of spirometry is more of a problem in that a doubling of the steroid dose has been shown to increase the peak expiratory flow by only 4.3 l min^{-1} (22). Bronchprovocation is, therefore, more appropriate. Figure 3 shows that there is a clear relationship between the dose of histamine to reduce the FEV_1 by 20% and the peak inspiratory flow through a Turbuhaler containing budesonide (23).

The data presented in Fig. 3 are consistent with gamma scintigraphy studies which highlight greater total lung deposition following inhalation of budesonide from a Turbuhaler using rates of 36 and 58 l min^{-1} (24). The mean (SD) total lung deposition was 14.8 (3.3) and 27.7 (9.5)%, respectively (24). Using terbutaline inhaled at 28 and 57 l min^{-1} through a Turbuhaler, another gamma scintigraphy study has demonstrated that the total lung deposition was 9.1 (1.5) and 16.8 (2.6)%, respectively (21). The data are consistent with the published comments that for the Tubuhaler device 'a direct relationship exists between peak inspiratory flow and lung deposition' (24) and that 60 l min^{-1} 'was the optimal inhalation rate for use through the Turbuhaler' (15,25). The lungs are the only route for the systemic delivery of fluticasone following inhalation. Measurement of the area under the curve from plasma fluticasone concentrations in 12 children inhaling fluticasone from a Diskus at inhalation flow rates of 35–74 l min^{-1} showed no difference (26). Thus, for the Diskus there is no effect due to inhalation rate which is consistent with the reported *in vitro* data (9–11).

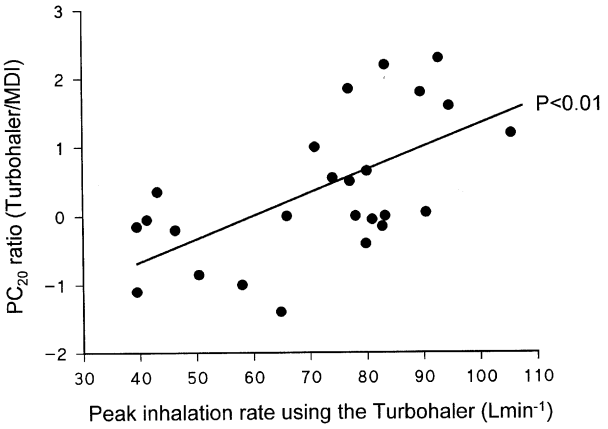

Fig. 3. The ratio for the change in the number of logarithmic doubling concentrations of histamine to reduce the FEV_1 by 20% (PC_{20} [FEV_1]) between inhalation of budesonide through a MDI and Turbuhaler plotted against the inhalation rate used with the Turbuhaler by 25 asthmatics. Reproduced with permission of Munksguard International Publishers Ltd (Copenhagen, Denmark) from Engel *et al.* Clinical comparison of inhaled budesonide delivered via pressurized metered dose inhaler or Turbuhaler®. *Allergy* 1989; 44: 220–225.

Long-acting beta agonists

In vitro studies using the I.S.F device (also known as the Cyclohaler and currently the Aerolizer—Novartis Pharmaceuticals) have demonstrated flow-dependent dose emission (27,28). An *in vivo* study has confirmed this phenomenon for the Aerolizer (29). Following inhalation of 12 μg of eformoterol, from an Aerolizer, the protective effect on the FEV_1 following exercise at 12 h post dose was measured in 16 children aged 8–15 years. After a placebo dose, the FEV_1 decreased by 34% after exercise, whilst after inhalation using a high flow rate it decreased by 15% compared to 23%, when a lower flow rate had been used.

In vitro studies have shown that other DPIs emit a dose which is independent of flow (9–11,27,28). The Diskus has demonstrated such a property (9–11), and a clinical study (30) using salmeterol through this device has shown no difference in the FEV_1 12 h post exercise when the dose was inhaled by children at flow rates of 30 and 90 l min^{-1}.

For some dry powder devices, low flow rates are slightly better than fast ones

In vitro (31,32) and clinical (33) studies using the Clickhaler together with lung deposition using gamma scintigraphy (34) and urinary pharmacokinetics methods (35) have shown that inhalation flow rate is a minor issue for this device with marginally better performance at lower flow rates. The results revealed that for salbutamol (31) and beclomethasone (32), the delivered dose was consistent over the range of inhalation rates routinely achieved by patients (35). A randomised, double-blind, placebo-controlled comparison of salbutamol inhaled, from a Clickhaler at 15, 30 and 60 l min^{-1} by 16 patients with stable asthma showed no difference in the bronchodilator response (33). Correlation of the *in vitro* (31,32) and clinical data (33) was strengthened by demonstration of similar relative lung deposition for salbutamol (35) although this index was slightly higher at 30 l min^{-1} compared to inhalation at 60 l min^{-1}. This latter study highlights the link to and importance of the respirable dose (35) The formulation with a high respirable dose provided a greater relative lung bioavailability than that with the low respirable dose formulation when inhaled at 30 and at 60 l min^{-1}. A comparison of the total lung deposition of radiolabelled beclomethasone inhaled from a Clickhaler showed that higher lung deposition was obtained at the lower flow rate (34). This study also revealed that the higher inspiratory flow rates through the DPI tended to result in greater central deposition.

Better lung deposition at a lower inhalation rate for a DPI has also been reported for the Spiros Inhaler (Dura Pharmaceuticals, U.S.A). At 60 l min^{-1} compared to 15 l min^{-1}, the mean (SD) total lung deposition for salbutamol was 19.3 (7.3) and 25.8 (9.2)%, respectively (36). For radiolabelled beclomethasone, in this device, the higher lung deposition at the lower inspiratory flow rate was accompanied by lower oropharyngeal deposition (37).

Inhalation rates by patients

Studies have shown (38–40) that the Rotahaler (GlaxoSmithKline) and Spinhaler(Rhone Poulenc Rorer) have a low resistance, whilst, the Diskhaler (GlaxoSmithKline) and Diskus together with the Aerolizer have a medium resistance, whereas the Clickhaler, Turbuhaler and an Easyhaler (Orion Pharma) together with a placebo version of the Twisthaler (Schering Plough) all have a high resistance. Studies have shown that there is a large inter-patient variability of inhalation rates when patients use a Diskus (41,42), Turbuhaler (41–44), Clickhaler (35,41) and Easyhaler (41,45).

Patients with COPD have been reported to have lower inhalation rates than adult asthmatics (41). This study also showed that asthmatic children (aged 5–16 years) achieved the highest inhalation rates, and that the more severe the restriction the lower were the inhalation rates through a variety of inhalers (41). Some studies (19,43) have recommended that the Turbuhaler device was not suitable for pre-school children because of the low flow achieved by this group. It has also been shown that the inhalation rates achieved by some patients (40) mirrors that of the resistance within each DPI device. Furthermore, Fig. 4 shows that there is a considerable intra-patient variability of inhalation rates when patients inhale through a Diskus (Accuhaler) and a Turbuhaler (46).

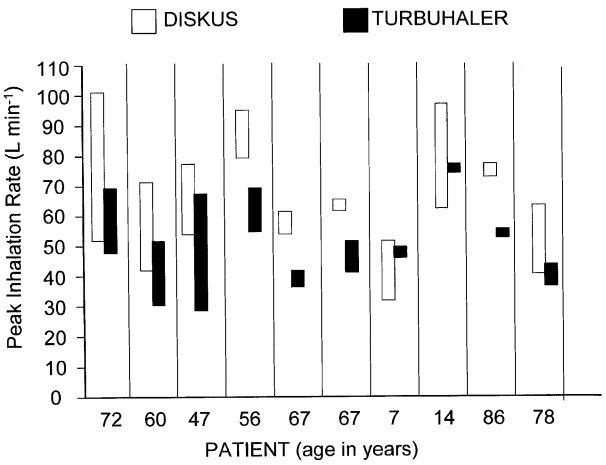

FIG. 4. The intra-individual variability of 10 patients when they inhale using a Diskus and Tubuhaler. Reproduced with permission of the BMJ Publishing Group from Tarsin *et al*. The intra-individual variability of inhalation rates through two different dry powder inhalers. *Thorax* 2000; 55 (Suppl 3): A61.

In Check Dial

Integration of all the above data highlights that there is a link between the emitted dose (in particular the respirable dose), total lung deposition and ultimately clinical response. The data also indicate that there is a difference in the emitted dose from DPIs with respect to the inhalation rate used and that for some devices this difference is clinically significant. Manufacturers should, therefore, be encouraged to label their product with the dose emitted at different flow rates. Intra- (46) and inter- (41) patient variability and a decreased inspiratory effort due to deterioration (47) may give rise to inconsistent dosing. Although the patient can compensate these inconsistencies when using their bronchodilator by titrating their dose with subjective response this cannot be applied to the corticosteroids.

The most desirable inhaler to prescribe for a patient is dependent on many factors. Asking the patient which they prefer is part of the process, but previously there has been no simple method of determining if the patient can use the chosen inhaler. The data above highlights the increased awareness of the role of inspiratory flow measurement as a tool in inhaler device selection (48). Some manufacturers have produced a peak inhalation rate meter for their own inhaler. The In-Check Dial has recently been introduced and contains the option to measure inhalation rates for a variety of inhalers. Studies have highlighted the potential of this meter to identify the inhalation rate, and thus inspiratory effort, of all types of patients using different DPIs [41,49–52]. In these studies, the In-Check Device has shown that only six (8%) out of 74 COPD patients (49) together with 48 (51) and 17 (52) children out of 64 (75%) and 57(30%), respectively, could generate an inspiratory flow of $> 60\,l\,min^{-1}$ when using the Turbuhaler. For the Turbuhaler device, it has been reported that $>60\,l\,min^{-1}$ is the most desirable rate (24) and *in vitro* studies (9–11) have highlighted high variability of the emitted dose below this inhalation rate. However, it can be argued that some clinical response is obtained between 30 and $60\,l\,min^{-1}$, through this device (19), but the clinical effect of the intra-individual variability of inhalation rates (46) is not known. Using the In-Check Dial, 14 out of 74 (19%) COPD patients (49) and three out of 19 (16%) asthamatics (19), could not generate the minimum ($30\,l\,min^{-1}$) inhalation rate required for the Tubuhaler. Only 19 out of 64 (30%) children could achieve the most desirable inhalation rate for the Aerolizer (51).

The inhalation rates obtained by 25 COPD patients when the In-Check Dial was set for an Aerolizer, Diskus, Turbuhaler, Clickhaler, placebo Twisthaler and an Easyhaler were all in the same order as the internal resistance in each device (40). Significant ($P<0.01$) correlations (46) have been found between the peak inhalation rate measured electronically, during characterisation of the inspiratory profile, and the In-Check Dial when patients inhaled through a Diskus and Turbuhaler. Thus, the In-Check Dial is an accurate method to identify inhalation rates and has been externally tested by AEA Technology (53). The initial velocity during an inhalation through a dry powder device has been reported to be the main factor which determines the respirable dose (54,55). Although the In-check Dial does not measure this parameter, a recent study has shown a correlation between the initial velocity when a patient uses an inhaler and the measured peak inhalation rate (56).

Although the emphasis for using the In-Check Dial is for DPIs, it also has the ability to measure the peak inhalation rate when there is no resistance to an inhalation. Thus, the patient's inhalation rate through a MDI or when it is attached to a spacer can be measured. If these rates are too high, then total lung deposition will be decreased and be concentrated in the central zones of the lungs (6,57). If these patients cannot slow down their inhalation rate, then a device with some resistance can be chosen.

Training inhaler technique is time consuming, thus is a cost issue, and studies have shown that for MDIs (1,2) and DPIs (3) patients revert back to their original technique. In the clinic, the In-Check Dial can be used to identify an inhaler they can use without training. Since there is an intra-patient variability of peak inhalation rates (46), a measurement in the middle of the most desirable range for an inhaler should be used. Of those which the meter identifies as suitable the patient can be asked to select which they would prefer. The patient can then be asked to inhale a dose through a placebo version, of this inhaler, without instruction. If the patient gets this last step correct, then the optimal inhaler is identified and no training on how to use it correctly should be necessary.

REFERENCES

1. Paterson IC, Crompton GK. Use of pressurised aerosols by asthmatic patients. *Br Med J* 1976 **1:** 76–77.
2. Crompton GK. Problems patients have using pressurised aerosol inhalers. *Eur J Respir Dis* 1982; **119:** (Suppl) 101–104.
3. Nimmo CJ, Chen DN, Martinusen SM, Ustad TL, Ostrow DN. Assessment of patient acceptance and inhalation technique of a pressurized aerosol inhaler and two breath-activated devices. *Ann Pharmacother* 1993; **27:** 922–927.
4. Larsen JS, Hahn M, Ekholm B, Wick KA. Evaluation of conventional press-and-breathe metered-dose inhaler technique in 501 patients. *J Asthma* 1994; **31:** 193–199.
5. Erickson SR, Horton A, Kirking DM. Assessing metered-dose inhaler technique: Comparison of observation v's patient self report. *J Asthma* 1998; **35:** 575–583.
6. Newman S, Steed K, Hopper G, Kallen A, Borgstrom L. Comparison of gamma scintigraphy and a pharmcokinetic technique for assessing pulmonary deposition of terbutaline sulphate delivered by pressurized metered dose inhaler. *Pharm Res* 1995; **12:** 231–236.
7. Chrystyn H. Anatomy and physiology in delivery: can we define our targets. *Allergy* 1999; **54:** 82–87.
8. Chrystyn H Is total particle dose more important than particle distibution. *Respir Med* 1997; **91** (Suppl. A): 17–19.

9. Palander A, Mattila T, Karhu M, Muttonen E. *In-vitro* comparison of three salbutamol-containing multidose dry powder inhalers. *Clin Drug Invest* 2000; **20:** 25–33.
10. Malton A, Sumby BS, Smith IJ. A comparison of *in-vito* drug delivery from tow multidose powder inhalation devices. *Eur J Clin Res* 1995: **7:** 177–193.
11. Malton A, Sumby BS, Dandiker Y. A comparison of *in-vito* drug delivery from salbutamol Diskus and terbutaline Turbuhaler inhalers. *J Pharm Med* 1996; **6:** 35–45.
12. Barry PW. Problems with inhalation drug delivery. PhD Thesis. University of Leicester, Leicester, 1999: 118–130.
13. Olsson B, Asking L, Borgstrom L, Bondesson F. Effect of inlet throat on the correlation between the fine particle dose and lung deposition. In: Dalby RN, Bryon PR, Farr SY (eds). *Respiratory Drug Delivery*, Vol. V. USA: Interpharm Press Inc. 1996; 273–281.
14. Sikstone VL, Dennis JH, Pieron CA, Chrystyn H. An investigation of *in-vitro*/*in-vivo* correlations for salbutamol nebulized by eight systems. *J Aerosol Med* 2002 (in press).
15. Borgstrom L, Derom E, Stahl E, Wahlin-Boll E, Pauwels R. The inhalation device influences lung deposition. *Am J Respir Crit Care Med* 1996; **153:** 1636–1640.
16. Newman SP, Talaee N, Clarke SW. Salbutamol aerosol delivery in man with the Rondo Spacer. *ActaTher* 1991, **17:** 49–50.
17. Johnsen CR, Weeke ER. Turbuhaler — a new device for dry powder terbutaline inhalation. *Allergy* 1988; **43:** 392–395.
18. Engel T, Scharling B, Skovsted B, Heinig JH. Effects, side effects and plasma concentration of terbutaline in adult asthmatics after inhaling from a dry powder inhaler device at different flows and volumes. *Br J Clin Pharmacol* 1992; **33:** 439–444.
19. Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow-rate upon the effect of a Turbuhaler. *Arch Dis Child* 1990; **65:** 308–310.
20. Hirsch T, Peter-Kern M, Koch R, Leupold W. Influence of inspiratory capacity on brochodilation of terbutaline via turbuhaler® or pressurised metered-dose inhaler in asthmatic children: a comparison. *Respir Med* 1997; **91:** 341–346.
21. Dolovich M, Vanzieleghem M, Hidinger K-G, Newhouse M. Influence of inspiratory flow rate (Vi) on the response to terbutaline (T) inhaled via the Turbuhaler (TH) *Allergy Proc*. 1988; **9:** 380.
22. Dahl R, Lundback B, Malo JL MD, Mazza JA, Nieminen MM, Saarelainen P, Barnacle H. A dose ranging study of fluticasone propionate in adult patients with moderate asthma. *Chest* 1993; **104:** 1352–1358.
23. Engel T, Heinig JH, Malling H-J, Scharling B, Nikander K, Madesen F, Clinical comparison of inhaled budesonide delivered either via pressurized metered dose inhaler or Turbuhaler®. *Allergy* 1989; **44:** 220–225.
24. Borgstrom L, Bondesson E, Moren F, Trofust E, Newman SP. Lung deposition of budesonide inhaled via Turbujaler® — a comparison with terbutaline sulfate in normal subjects. *Eur Respir J* 1994; **7:** 69–73.
25. Agertoft L, Pedersen S. Influence of inspiratory flow rate on plasma levels and lung deposition of fluticasone properties inhaled from Diskus Dry Powder Inhaler. *Eur Respir J* 1999; **14** (Suppl. 30): 1264
26. Nielsen KG, Skov M, Klug B, Ifversen M, Bisgaard H. Flow-dependent effect of formoterol dry-powder inhaled from an Aerolizer. *Eur Respir J* 1997; **10:** 2105–2109.
27. Newman SP, Moren F, Trofast E, Talaee N, Clarke SW. Terbutaline sulfate Turbuhaler — effect of inhaled flow-rate on drug deposition and efficacy. *Int j Pharm* 1991; **74:** 209–213.
28. Steckel H, Muller BW. *In-vitro* evaluation of dry powder inhalers I: drug deposition of commonly used devices. *Int J Pharm* 1997; **154:** 19–29.
29. Srichana T, martin GP, Marriott C, Dry powder inhalers. The influence of device resistance and powder formulation on drug and lactose deposition *in vitro*. *Eur j pharm Sci* 1998; **7:** 73–80.
30. Nielsen KG, Auk IL, Bojsen K, Ifversen M, Klug B, Bisgaard H. Clinical effect of Diskus dry-powder inhaler at low and high inspiratory flow-rates in asthmatic children. *Eur Respir J* 1998; **11:** 350–354.
31. Barrowcliffe j, McGlynn P, Tickle S, Sandbank F, Wong T. The *in-vitro* evaluation of a novel multi-dose dry powder inhaler. In: The Aerosol Society (eds), *Drug Delivery to the Lungs*, Vol. VII. The Aerosol Society, Bristol. December 1996: 82–85.
32. Barrowcliffe J, McGlynn, Ratcliffe S, Sewell M, Sheikh S. Walters M. Beclomethasone dispropionate (BDP) Clickhaler™. *In vitro* performance of a sterod *novel* dry powder inhaler. In: The Aerosol Society (eds), *Drug Delivery to the Lungs,* Vol. VIII. The Aerosol Society, Bristol. December 1997: 125–128.
33. Newhouse MT, Nantel MP, Chambers CB, Pratt B, Parry-Bilings M. Clickhaler (a novel dry powder inhaler) providing similar brochodilation to pressurized metered dose inhaler, even at low flow rates. *Chest* 1999; **115:** 952–956.
34. Warren SJ, Taylor G. Effect of inhalation flow profiles on the deposition of radiolabelled BDP from a novel dry powder inhaler (DPI, Clickhaler™), a conventional metered dose inhaler (MDI) and MDI plus spacer. In: Dalby RN, Byron PR, Farr SY (eds). *Respiratory Drug Delivery,* Vol. VI. USA: Interpharma. Press Inc., 1998; 453–455.
35. Chege JK, Chrystyn H. The relative bioavailability of salbutamol to the lung using urinary excretion following inhalation from a novel dry powder inhaler: the effect of inhalation rate and formulation. *Respir Med* 2000; **94:** 51–56.
36. Hill M, Vaughan L, Doovich M. Dose targeting for dry powder inhalers. In: Dalby RN, Byron PR, Farr SY (eds). *Respiratory Drug Delivery,* Vol. V. USA: Interpharma. Press Inc. 1996; 197–208.
37. Warren S, Taylor G, Godfrey C, Cote G, Hill M. Gamma scintigraphy evaluation of beclomethasone dipropionate (BDP) from the Spiros® Dry Powder Inhaler. *J Aerosol Med* 1999; **12:** A117.
38. Clark AR, Hollingworth AM. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers — implications for *in-vitro* testing. *J Aerosol Med* 1993; **6:** 99–106.
39. Richards R, Saunders M. Need for a comparative performance standard for dry powder inhalers. Thorax 1993; **48:** 1186–1187.
40. Tarsin W. Assi K, Corrado OJ, Chrystyn H. Measurement of patient inhalation rates for different dry powder inhalers (DPIs) using the In-Check Dial *Thorax* 2000; **55** (Suppl. 3): A63.
41. Tarsin W, Corrado OJ, Brownlee. K, Kanthapillai P, Pearson S, Chetcuti P, Chrystyn H. Inter-individual variability of peak inhaltion rates through different inhalers by asthmatic children and adults and those with COPD. *Eur Respir J* 2001; **18** (Suppl. 33); 133s.
42. Bisgaard H, Klug B, Sumby BS, Burnell, PKP. Fine particle mass from the Diskus inhaler and Turbuhaler inhaler in children with asthma. *Eur Respir J* 1998; **11:** 1111–1115.
43. Bisgaard H, Pedersen S, Nikander K. Use of budesonide Turbuhaler® in young children suspected of asthma. *Eur Respir J* 1994; **7:** 740–742.
44. Hawksworth GM, James L, Chrystyn H. Characterisation of the inspiratory manoeuvre when asthmatics inhale through a Turbuhaler pre and post counselling in a Community Pharmacy. *Respir Med* 2002; **94:** 501–504.
45. Malmstrom K, Sorva R, Silvasti M. Application and effficacy of the multidose powder inhaler, Easyhaler®, in children with asthma. *Pediatr Allergy Immunol* 1999; **10:** 66–70.
46. Tarsin W. Hawksworth GM Chrystyn H. The intra-individual variability of inhalation rates through two different dry powder inhalers. *Thorax* 2000; **55** (Suppl. 3): A61.

47. Andersen PB, Stahl E, Hansen NCG. Terbutaline via Turbuhaler® is effective in reversing methacholine-induced bronchoconstriction. *J Chem Res* 1998, **1:** 49–54.
48. Pearce L. The measurement of inspiratory flow in clinical practice. *Drug Delivery to the Lungs,* Vol. XI. The Aerosol Society, In: The Aerosol Society (ed) Bristol, December 2000: 102–104.
49. Nsour W, Alldred A, Corrado OJ, Chrystyn H. Measurement of peak inspiration rates with an In-Check meter to identify an elderly patient's ability to use a Turbuhaler. *Respir Med* 2001; **95:** 965–968.
50. Brajnik UA, Sakharova GM, Makrestskaja ON Belevsky AS, Chuchalin AG. The role of inspiratory flow measurement in a choosing suitable inhaler device in asthmatics patients. *Eur Resp J* 2000; **16** (Suppl. 31): 316s.
51. Emeryk A, Bartkowiak-Emeryk M, Kokot I. Assessment of inspiratory flow rate (PIFR) is advisable before choosing a dry powder inhaler for treatment of asthmatic children. *Eur Resp J* 2000; **10** (Suppl. 31): 540s.
52. Amirav J, Newhouse MT. Measurement of PIF with the In-Check Dial device to simulate low resistance (Diskus) and high resistance (Turbuhaler) DPIs in children with asthma. *Eur Resp J* 2000; 540s:P540s.
53. www.Clement-clarke.com/inspiratory/In-check
54. de Boer AH, Winter HMI, Lerk CF. Inhalation characteristics and their effects on *in vitro* drug delivery from dry powder inhalers. Part 1. Inhalation characteristics, work of breathing and volunteer's preference in dependence of the inhaler resistance. *Int J Pharm* 1996; **130:** 231–244.
55. Everard ML, Devadason SG, Le Soeuf PN. Flow early in the inspiratory manoeuvre affects the aerosol particle size distribution from a Turbuhaler. *Respir Med* 1997; **91:** 624–628.
56. Broders MEAC, Molema J, Vermue NA, Folgering HThM. Peak inspiratory flow rate and slope of inhalation profiles in dry powder inhalers. *Eur Respir J* 2001; **18:** 78–783.
57. Farr SJ, Rowe AM, Rubsamen R, Taylor G. Aerosol deposition in the human lung following administration from a microprocessor-controlled pressurized metered-dose inhaler. *Thorax* 1995; **50:** 639–644.