ELSEVIER

International Journal of Pharmaceutics 107 (1994) 211–217

international journal of pharmaceutics

The optimal particle size for β-adrenergic aerosols in mild asthmatics

Pieter Zanen *, Liam T. Go, Jan-Willem J. Lammers

Department of Pulmonary Diseases, University Hospital Utrecht, PO Box 85500, 3508 GA, Utrecht, The Netherlands

(Received 26 November 1993; Accepted 19 January 1994)

Abstract

Background: the optimal particle size of a β_2-mimetic aerosol is not known. Methods: eight stable asthmatics with a FEV_1 (forced expiratory volume) of 72% of the predicted value inhaled three types of monodisperse salbutamol aerosols, with particle sizes of 1.5, 2.8 and 5 μm, respectively, and a placebo aerosol. The volunteers inhaled cumulative dosages of 5, 10, 20 and 40 μg salbutamol, after which lung function improvement was determined. The four resulting dose-response curves (one for each type of aerosol) were analysed with repeated measurements ANOVA. Results: for the FEV_1 and the $MEF_{75/50/25}$ (maximum expiratory flow) the 2.8 μm aerosol induced a significantly better dilation than the 5 μm aerosol. In the case of the PEF (peak expiratory flow) the 1.5 μm aerosol elicited a significantly smaller improvement than the 2.8 μm aerosol. No particle size effect was noticeable in the case of the VC (vital capacity), FVC (forced vital capacity) and the R_{tot}. Conclusions: in mild asthmatics the particle size of choice for a β_2-mimetic aerosol should be around 2.8 μm.

Key words: Aerosol; Particle size; Salbutamol; Lung function testing; Spinning top generator

1. Introduction

The treatment of asthma and chronic obstructive pulmonary diseases (COPD) has improved considerably with the introduction of drugs by inhalation. As compared to oral administration, dosages can be decreased substantially and the incidence of side effects is diminished considerably. Unfortunately, the currently available inhalation preparations show one major disadvantage: only a small quantity of the administered mass reaches the airways (Clarke, 1986). Part of the problem is caused by the fact that, to date, only highly polydisperse aerosols are available. Such aerosols contain large particles, which are not effective, since they deposit extrathoracically.

The site of deposition of the particles in the airways depends strongly on the way of inhalation and the size of the particles. Targeting of deposition can be achieved by adjusting the inhalation manoeuvre and the particle size. A way to improve the efficacy therefore is to determine the optimal particle size (Byron, 1987). An adequately targeted β_2-mimetic agent will induce the strongest decrease in airway obstruction. The deposition patterns of aerosols in the lung will be

* Corresponding author.

SSDI 0378-5173(94)00028-4

influenced, however, by the degree of constriction of the airways. Consequently, one is forced to stratify patients. A number of studies have focused on the relationship between particle size of a β_2-mimetic aerosol and its efficacy (Rees and Clark, 1982; Clay et al., 1986; Mitchell et al., 1987; Patel et al., 1990; Hultquist et al., 1992). However, it is impossible to conclude from these studies the optimal particle size, since the results of the various investigations are contradictory.

To determine the optimal particle size we compared the effects of salbutamol aerosols with variable diameters on the degree of lung function improvement in a group of asthmatic patients with mildly impaired lung function. To do so, we used monodisperse aerosols because polydisperse aerosols contain overlapping particle size distributions, which will obscure differences between larger and smaller particles.

2. Materials and methods

2.1. Patients

Eight mild asthmatic patients participated in the trial (three women and five men). The average age (SD) was 40 (10) years, and the mean FEV_1 (SD) was 72.3% (6.8%) of the predicted value. In all patients a bronchodilator response of $\geq$ 15% after inhalation of 200 μg salbutamol had been measured just before the trial. None of the patients were smokers. All patients used corticosteroids by inhalation; cromoglycate or long-acting β_2-mimetic agents were not used. Oral antiasthma medication was not allowed. Except for the corticosteroids, their regular medication was discontinued 6–8 h before the start of the trial. All patients gave their written consent before entering the trial, which was approved by the hospital ethics committee.

2.2. Aerosol generation

Monodisperse aerosols (geometric SD < 1.2) were produced by a spinning top generator (Cheah and Davies, 1984). A spinning top generator consists of a small disk, rotating at 12000 rpm. Liquid is fed to the centre of the disk and the high centrifugal force causes droplets to leave the rim of the disk. These droplets are all of the same size. These droplets are dried by hot air and led to a small tank, from which the patients inhale. The diameter of the resulting dry particles is governed by the concentration of the drug in the solution and its viscosity. Salbutamol solutions (50% water/50% ethanol) of 0.1, 1 and 10% were used to yield aerosols with a mass median aerodynamic diameter (MMAD) of 1.5, 2.8, and 5 μm, respectively. Each time a patient was due to start aerosol inhalation, the mass of salbutamol per l of air and the particle diameter of the dry aerosol particles in the tank were measured by an Aerodynamic Particle Sizer 33 (TSI, St. Paul, MN). For each dose the volume of air inhaled was calculated by dividing the dose by the mass of salbutamol per l of air. If sufficient aerosol-containing air had been inhaled, the aerosol inhalation was discontinued by switching over to non-aerosol containing air.

2.3. Procedure

Each patient was studied at the lung function laboratory with intervals of 1 week. The baseline FEV_1 during each session was not allowed to vary more than 10%. Each session consisted of four cycles, which involved measurement of the lung function 15 and 30 min after administration of the aerosol. A subsequent cycle started within 5 min after the previous one. First, 5 μg salbutamol was administered. This was followed by 5, 10 and 20 μg during the second, third and fourth cycle, respectively, resulting in cumulative doses of 5, 10, 20 and 40 μg salbutamol (all dosages are expressed as μg delivered to the mouth). The inhalation manoeuvre consisted of inhalation of the slow vital capacity with a flow of 40–60 l/min, followed by a breath-holding period of 10 s and a slow exhalation. The inhalation flow and volume were measured by a hot wire anemometer placed close to the mouth of the patient. The amount of aerosol deposited in the anemometer was negligible. Before aerosol inhalation, the patients were taught to inhale and had the opportunity to correct the inhalation flow by watching an indicator

connected to the anemometer. Administration of the aerosols was carried out in a randomized single-blind manner (the author P.Z. operated the spinning top generator). On the first day, a placebo aerosol was administered in order to facilitate early detection of any adverse reactions of the patient to equipment or solvents. In addition, the placebo measurement served to determine the spontaneous variability in airway obstruction during the measuring period.

2.4. Lung function assessment

The lung function was assessed 15 and 30 min after inhalation of the aerosol. The lung function assistant was not informed about the type of aerosol administered. The R_{tot} was measured with a body plethysmograph, the FEV_1, FVC, and VC by means of spirometry, and the PEF and $MEF_{75/50/25}$ were derived from maximal expiratory flow-volume curves.

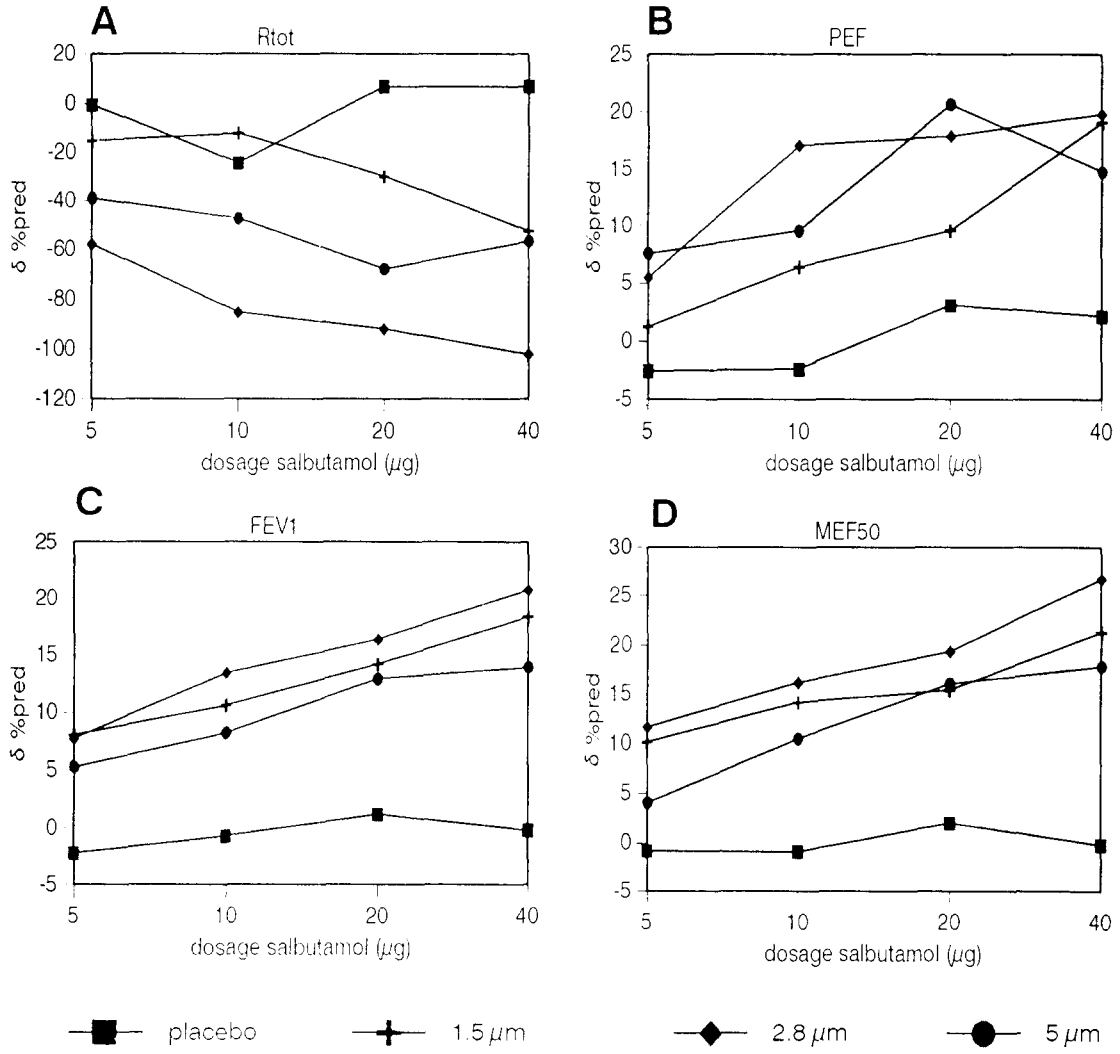

Fig. 1. (a–d) Graphs showing the dose-response curves for R_{tot}, PEFR, FEV_1 and MEF_{50}. Dosages (μg) are depicted as cumulative numbers; the response is the change as percentage of the predicted value. (■) Placebo, (+) 1.5 μm aerosols, (◆) 2.8 μm aerosols and (●) 5 μm aerosols.

2.5. Statistics

The change in lung function was expressed as a percentage of the predicted value. Four dose-response curves were generated, one for each type of aerosol. These dose-response curves were analyzed for effects related to the type of aerosol (aerosol-size effect), effects of increasing dosages (dose effect), and interaction between size and dosage using repeated measurements ANOVA (Girden, 1992). Any differences between the measurements at $t = +15$ min and $t = +30$ min were evaluated with the paired t-test.

The mean lung function improvement over all four dosages will be higher for the most potent aerosol as compared to the less potent aerosols. In order to determine whether a less potent aerosol deviates significantly from the most potent aerosol, it was calculated how large the deviation between these means should be before it would be appropriate to speak of significance. In this respect, the method of Schuirmann (1987) was applied, which is comparable to the LSD test. In all calculations an α-value of 0.05 was considered to be significant.

3. Results

All eight patients completed the four sessions. None of the values of the lung function parameters, measured 30 min after administration of the aerosol, differed significantly from those measured 15 min after administration. Therefore, only an evaluation is given of the measurements conducted 15 min after aerosol administration.

In Fig. 1a–d the dose-response curves for R_{tot}, PEF, FEV_1 and MEF_{50} are presented. In none of the parameters was any change was measured during the inhalation of placebo. The evaluation of the dose effects demonstrated that for all lung function parameters statistically significant differences existed between dosages, with the higher dosages causing a stronger bronchodilation ($p < 0.05$). The interaction between the dose and the effects of the three types of salbutamol aerosols was non-significant for all lung function parameters ($p > 0.1$), which indicates that the dose-response curves run parallel.

In evaluating the aerosol-size effect, the analysis of variance demonstrated significant differences with reference to placebo for FEV_1 ($p < 0.01$), PEF ($p < 0.01$), FVC ($p < 0.01$), MEF_{75} ($p < 0.01$), MEF_{50} ($p < 0.01$) and MEF_{25} ($p < 0.01$). This implies that all the dose-response curves of the salbutamol aerosols are located higher than the placebo curves. For R_{tot} ($p = 0.116$) and VC ($p = 0.068$) no significant differences due to the different aerosol sizes were demonstrable. The reason for this is to be found in the strong spontaneous variability of R_{tot} and/or the minor improvement of VC.

A significant difference with reference to the 2.8 μm aerosol will occur for FEV_1 if the deviation between the means exceeds 2.9%; for PEF this deviation should be at least 5.9%, for $MEF_{75/50/25}$ at least 5.4, 4.3 and 4.9%, respectively, and, finally, for FVC at least 9.4%. In the case of FEV_1 and $MEF_{75,50,25}$ a statistically significant difference occurred between the 5 and 2.8 μm aerosols. For PEF a significant difference was found between the 1.5 and 2.8 μm aerosols. For FVC the differences were too small to be significant.

Table 2 also lists the mean improvements as % predicted with 95% confidence intervals after administration of 40 μg salbutamol for all lung function parameters. Despite the low dosage, a

Table 1
Mean (SD) improvement in lung function (% predicted) over all four dosages listed per type of aerosol

Lung function parameter	Particle size of the aerosol			Significant different aerosols
	1.5 μm	2.8 μm	5 μm	
FEV_1	12.8 (4.3)	14.6 (6.5)	10.1 (4)	2.8 vs 5
FVC	8.9 (5.6)	9.6 (9.3)	7.9 (6.6)	NS
MEF_{25}	12.1 (6.6)	14.9 (9.5)	9.2 (7.9)	2.8 vs 5
MEF_{50}	15.2 (6.7)	18.5 (9.4)	12.1 (6.2)	2.8 vs 5
MEF_{75}	17 (4.4)	21.4 (9)	14.6 (5.6)	2.8 vs 5
PEF	9 (7.1)	15 (7)	13.1 (7.9)	2.8 vs 1.5
R_{tot}	−27.6 (93)	−84.3 (92)	−52.7 (62.1)	NS
VC	7 (7.8)	8.1 (9.4)	6 (8.9)	NS

significant improvement of the lung function can be observed. The improvement in the VC was not significant.

None of the patients reported any adverse effects as a result of the experiment.

4. Discussion

The increase in FEV_1 and $MEF_{75/50/25}$ after the 5 μm aerosol differed significantly from that of the 2.8 μm aerosol, while there were no significant differences between the 1.5 and 2.8 μm aerosols. The increase in PEF was greatest after the 2.8 μm aerosol, not being significantly different from the 5 μm aerosol. No size effect was present in the case of VC, FVC and R_{tot}. We were able to show these differences in a relatively small group of volunteers. This is due to a low intrasubject variability and the use of repeated measurement ANOVA, which eliminates the interindividual variability. Patel et al. (1990) also demonstrated comparable differences in a small group of volunteers.

The lung has the capacity to intercept a large portion of the inhaled particles rapidly and effectively by several mechanisms that cause particles to deposit on the mucous membrane. Two important processes in this context are impaction and sedimentation (Lippmann et al., 1980). Impaction means that particles are not able to follow changes in the direction of the air stream and deposit. This mechanism is of particular relevance for large or heavy particles. Sedimentation is a time-dependent process related to the velocity at which particles fall under the influence of gravitation. The speed of fall becomes constant at the moment the resistance of the air is equal to gravitation. These two mechanisms cause large particles to deposit in the upper airways, whereas smaller particles escape from impaction and penetrate the airways more deeply. Therefore, a deposition pattern in the airways is evident. Targeting the deposition towards a segment of the airways can be achieved by selecting the appropriate particle size of the aerosol or by adjustment of the breathing technique (Byron, 1987).

It is possible that, in the efficacy of β_2-mimetic agents, a significant role is played by the fact that the β_2-receptors are not uniformly distributed in the airways. In a number of publications, an increase in the number of receptors has been reported in association with distances further into the periphery of the lung (Barnes et al., 1982, 1983). Assuming that a greater effect is obtained when the concentration at the receptor is higher, there is a ratio for matching the deposition pattern of β_2-mimetics to the β-adrenoceptor distribution.

In the present study, we have based ourselves on the assumption that a more peripheral deposition was desirable. One way to achieve this is by the slow and deep inhalation of the aerosols. In addition, the particles were reduced in size. Reduction in size, however, cannot be continued without impunity. Excessively small particles are known to have a terminal velocity that is so low that they hardly deposit. This implies that there is an ideal particle size: not too large and not too small. The optimal particle size will depend on a number of factors, i.e., the preferred deposition pattern, the condition of the airways – in this context their diameter – and the inhalation technique. We decided on an upper limit of 5 μm, since various studies have demonstrated that particles with an MMAD above 5 μm only reach the airways to a limited extent (Svartengren et al., 1991). The lower limit of 1.5 μm was chosen on technical grounds (since both the spinning top generator and the aerodynamic particle sizer are characterized by a functional lower limit of 0.5–1 μm), and it has been documented that particles with an MMAD below 0.5 μm scarcely deposit in the airways (Lippmann et al., 1980).

In asthmatics Clay et al. (1986) found that a 1.8 μm terbutaline aerosol induces a stronger bronchodilatation than a 4.6 or a 10.3 μm aerosol, whereas Patel et al. (1990) observed that a 2.5 μm isoproterenol aerosol is more potent than a 5 μm aerosol. Johnson et al. (1989) observed a significant difference between a 3.3 and a 7.7 μm salbutamol aerosol, as did Ruffin et al. (1986) between a 1.5 and a 3.2 μm isoproterenol aerosol; the outcome of both studies was in favour of the smaller aerosol. However, from all these data, it is not feasible to derive an optimal aerosol diam-

eter. Moreover, the matter is complicated by the negative findings of Hultquist et al. (1992) and Mitchell et al. (1987): neither group of investigators found any differences in potency between 1.5 and 4.8 μm aerosols and 1.4 and 5.5 μm aerosols, respectively.

The results of our study demonstrate that in asthma patients with a mild airway obstruction an aerosol with an MMAD of around 2.8 μm is to be preferred. The results of our study confirm the conclusion drawn by Patel et al. (1990) that a 2.5 μm aerosol is more potent than a 5 μm aerosol, but additionally demonstrate that smaller aerosols are of no benefit. At the same time, an explanation has been found for the negative findings of Mitchell et al. (1987) and Hultquist et al. (1992). Both groups of investigators selected aerosol diameters that led to minor differences in potency. The discrepancy between these and other investigators thus is merely an apparent one, attributable to the choice of particle sizes. The results obtained by Clay et al. (1986) are not easy to explain: however, in that study the aerosols were administered by means of various nebulisers. It is possible that these nebulisers released divergent dosages, which might be interpreted as differences in potency.

The results of our study can be explained as follows: particles of 5 μm will be deposited extrathoracically to a greater extent than smaller particles, which are able to penetrate the airways deeply (in the case of the 1.5 μm aerosol the smallest amount can be expected extrathoracically). Hence, small particles are to be preferred for deep penetration. However, such particles deposit in minute quantities, so deep penetration is at the expense of a lower mass deposited (Lippmann et al., 1980). As for PEF, it is striking that the 5 μm particles perform better than those of 1.5 μm: the bulk of the 1.5 μm particles pass the central and extrathoracic compartments. Here, we see a contrast with the more peripherally oriented lung function parameters: the 5 μm aerosol is inferior to the other two. The 5 μm aerosol reaches the peripheral compartment to a lower degree. The lower potency of the 1.5 μm aerosol can be ascribed to its limited tendency to deposit. The fact that in all cases 2.8 μm particles induce a better effect than 5 μm particles can be attributed to the difference in extrathoracic deposition (Gonda, 1981). We did not measure the deposition patterns of these aerosols within the lung. Therefore, we are not certain whether the differences in potency can be ascribed to a better matching between the β_2-receptor distribution and deposition. However, it can be stated that the results of this investigation are in line with theoretical predictions of deposition patterns (Gonda, 1981). The deposition of particles is never confined to a small segment of the airways: one always encounters wide patterns. The calculations of Gerrity et al. (1979) show that in many segments of the airways comparable number of particles will deposit, while the changes in the patterns due to differences in particle size are not overwhelming. In asthmatics the same conclusions were drawn by Kim et al. (1983). We therefore feel that the considerable extrathoracical deposition of large particles and the low extent of deposition for smaller particles, combined with an inherently low degree of deposition for very small particles offer a good explanation for our results, without taking the receptor distribution into account.

In agreement with Patel et al. (1990) and Mitchell et al. (1987), we conclude that it is possible to induce adequate bronchodilation with very small dosages. In Table 2 we have included the data on the improvement of lung function after 40 μg salbutamol. This dosage is only one-fifth of frequently used MDI dosages and one-

Table 2
Mean improvement in lung function (% predicted) following 40 μg salbutamol administered as a 2.8 μm aerosol

Lung function parameter	Improvement in % predicted	95% confidence interval	
FEV_1	20.7	13.5	28.0
FVC	12.6	2.4	22.7
MEF_{25}	26.9	20.6	36.9
MEF_{50}	26.7	18.5	34.8
MEF_{75}	28.8	16.4	37.6
R_{tot}	−102.2	−29.0	−175.0
PEF	19.8	12.4	27.1
VC	9.3	0.11	18.7

tenth of the dosages usually administered by dry-powder inhalation (DPI). These low dosages lead to such a distinct bronchodilation because they are monodisperse, in contrast to the aerosols administered by metered-dose or dry-powder inhalers. In the usual polydisperse aerosols only a minor fraction (depending on the formulation) of the mass will consist of particles < 2.8 μm. The larger particles are less active, so that the effective dosage is low. As mentioned before these large particles deposit in the upper airways. However, the side effects, due to this upper airway deposition, will be acceptable. If the same reduction in dose is possible with corticosteroids the advantages are evident.

We conclude that in mild asthmatics the mean particle diameter of a β_2-mimetic aerosol should be around 2.8 μm for optimal improvement of the lung function. The dosage of salbutamol can be reduced for such aerosols.

Acknowledgments

We thank Mrs H.M.J. Monrooij-van der Molen for help in measuring lung function, Mrs A. Vonk for assistance with this article and Mr A. Plomp for help in mastering the spinning top generator.

References

Barnes, P.J., Basbaum, C.B. and Nadel, J.A., Autoradiographic localization of autonomic receptors in airway smooth muscle. *Am. Rev. Respir. Dis.*, 127 (1983) 758–762.

Barnes, P.J., Basbaum, C.B., Nadel, J.A. and Roberts, J.M., Localization of ß-receptors in mammalian lung by light microscopic auto-radiography. *Nature*, 299 (1982) 444–447.

Byron, P.R., Pulmonary targeting with aerosols. *Pharm. Technol.*, 11 (1987) 42–56.

Cheah, P.K.P. and Davies, C.N., The spinning top aerosol generator-improving the performance. *J. Aerosol. Sci.*, 15 (1984) 741–751.

Clarke, S.W., Aerosols as a way of treating patients. *Eur. J. Respir. Dis.*, 69 (Suppl. 146) (1986) 525–533.

Clay, M.M., Pavia, D. and Clarke, S.W., Effect of aerosol particle size on bronchodilation with nebulised terbutaline in asthmatic patients. *Thorax*, 41 (1986) 364–368.

Gerrity, T.R., Lee, P.S., Hass, F.J., Marinelli, A., Werner, P. and Lourenco, R.V., Calculated deposition of inhaled particles in the airway generations of normal subjects. *J. Appl. Physiol.*, 47 (1979) 867–873.

Girden, E.R., *ANOVA: Repeated Measures*, Sage, Newbury Park, 1992.

Gonda, I., A semi-empirical model of aerosol deposition in the human respiratory tract for mouth inhalation. *J. Pharm. Pharmacol.*, 33 (1981) 692–696.

Hultquist, C., Wollmer, P., Eklundh, G. and Jonson, B., Effect of inhaled terbutaline sulphate in relation to its deposition in the lungs. *Pulm. Pharm.*, 5 (1992) 127–132.

Johnson, M.A., Newman, S.P., Bloom, R., Talee, N. and Clarke, S.W., Delivery of albuterol and ipratropiumbromide from two nebulizer systems in chronic stable asthma. *Chest*, 96 (1989) 6–10.

Kim, C.S., Brown, L.K., Lewars, G.G. and Sackner, A.A., Deposition of aerosol particles and flow resistance in mathematical models and experimental airway models. *J. Appl. Physiol.*, 55 (1983) 154–163.

Lippmann, M., Yeates, D.B. and Albert, R.E., Deposition, retention and clearance of inhaled particles. *Br. J. Ind. Med.*, 37 (1980) 337–362.

Mitchell, D.M., Solomon, M.A., Tolfree, S.E.J. and Spiro, S.G., Effect of particle size of bronchodilator aerosols on lung distribution and pulmonary function in patients with chronic asthma. *Thorax*, 42 (1987) 457–461.

Patel, P., Mukai, D. and Wilson, A.F., Dose-response effects of two sizes of monodisperse isoproterenol in mild asthma. *Am. Rev. Respir. Dis.*, 141 (1990) 357–360.

Rees, P.J. and Clark, T.J.H., The importance of particle size in response to inhaled bronchodilators. *Eur. J. Respir. Dis.*, 63 (Suppl. 119) (1982) 73–78.

Ruffin, R.E., Dolovich, M.B., Oldenburg, F.A. and Newhouse, M.T., The preferential deposition of inhaled isoproterenol and propanolol in asthmatic patients. *Chest*, 80 (1986) 904–907.

Schuirmann, D.J., A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokinet. Biopharm.*, 15 (1987) 657–680.

Svartengren, M., Anderson, M., Bylin, G., Philipson, K. and Camner, P., Mouth and throat deposition of 3.6 μm radiolabelled particles in asthmatics. *J. Aerosol. Med.*, 4 (1991) 313–321.