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An in vitro evaluation of various spacer devices for metered-dose inhalers using the Twin Impinger

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Abstract

Spacer devices are a useful tool in inhalation therapy with metered-dose inhalers (MDI). Various spacers with different shapes and sizes are currently on the market. This study intends to evaluate nine commercial spacers for use with MDIs. These devices were tested in combination with two different cromolyn-sodium MDIs. The assessment has been carried out using the Twin Impinger. The fractions of the dose remaining in actuator and spacer and the fractions delivered to stage 1 ($D_{50\%} > 6.4$ μm) and stage 2 ($D_{50\%} < 6.4$ μm) of the Twin Impinger were calculated and compared to a control experiment without spacer. Deposition in stage 1 is significantly reduced for all spacers. The differences indicated that the spacers are not equivalent. Some spacers increase the fraction of the dose delivered to stage 2 whereas others strongly reduce this fraction. This effect appears to be independent of spacer volume but depends on spacer and valve construction.

Key words: Spacer device; Valve; In vitro evaluation; Metered dose inhaler; Particle deposition; Twin Impinger; Aerosol

1. Introduction

Metered dose inhalers are widely used in the treatment of various respiratory diseases and have been accepted as an inexpensive, effective and easy to use method of therapy. However, it has been shown in vivo that only as little as 9% of the dose delivered is deposited in the lungs (Newman et al., 1981a).

The major drawbacks in MDI therapy are the problem of hand-to-mouth co-ordination for some patients (Crompton, 1982), the high initial velocity of the aerosol cloud leaving the actuator (Rance, 1974) and the large size of the primary droplets emitted. The large size and high speed of the droplets lead to considerable losses in the oropharynx (Moren and Andersson, 1980). These problems can be overcome, at least to some extent, by using auxiliary spacer devices being placed between patient and MDI actuator (Byron, 1990). Spacers have a number of advantages: they will provide additional time and heat for the propellant to evaporate. Thus, primary droplet size is reduced. Larger droplets settle in the spacer or impact on its walls. Additionally, droplet velocity

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will slow down substantially as the actuator is placed further from the mouth (Moren, 1978; Vidgren et al., 1987). Thereby impaction at the back of the throat will decrease and side effects seen with some drugs can be reduced (Brown et al., 1990). Last but not least, up to 70% of the patients fail to co-ordinate actuation and inhalation correctly (Gayrard and Orehek, 1980). This is easier when a spacer is used.

To date, a number of spacer studies have been carried out (e.g., König, 1985; Newman, 1985; Newman et al., 1981b, 1984, 1989). However, most of these dealt with the efficacy of drug administered by MDI alone vs MDI plus spacer. The aim of the present study is to compare various spacer devices currently on the market and to determine whether there are any significant differences or whether the devices are more or less equivalent as might be expected from such simple devices.

Although spacers generally look very similar, they differ in size (approx. 300–880 ml) and shape (ball, pear, cone, or tube). Additionally, some have a valve to keep particles from flying straight through the device.

The Twin Impinger (Hallworth and Westmoreland, 1987) with its mean nominal cut-off diameter ($D_{50\%}$) of 6.4 μm is a useful and convenient device to assess in vitro deposition differences (Phillips et al., 1990) despite the general problems of in vivo and in vitro correlation (Martonen et al., 1992). In the present model, stage 1 resembles the mouth, throat and upper respiratory system while stage 2 represents the lower respiratory tract. An optimal spacer would reduce the fraction in stage 1 to zero while the amount in stage 2 would increase. For the purpose of this study, particles with an aerodynamic diameter (D_{ae}) below 6.4 μm are considered 'respirable'.

2. Materials and methods

Tetrabutylammonium hydrogen sulfate (reagent grade) was obtained from Fluka Chemika (Buchs, Switzerland). Cellulose nitrate filters (0.45 μm) were from Sartorius (Göttingen, Germany). Methanol (HPLC grade) and potassium dihydrogen phosphate (reagent grade) were obtained from Merck (Darmstadt, Germany).

Table 1
Shape, size and type of valve of the spacers

Spacer	Shape	Volume (ml)	Valve system
Inhacort (normal)	pear	305	–
Inhacort (telescope)	pear	325	–
Viarox	pear	420	–
Aru	pear	530	–
Rondo	ball	300	plastic flap
Fisonair	cone	855	rubber membrane
Nebulator	cone	770	'lid'
Beclomet	cone	815	'lid'
Volumatic	cone	880	'lid'

2.1. Spacers

In this study nine spacers were tested (see Table 1). The Aru Spacer (Ankerpharm, Rudolstadt, Germany), conventional and telescope-like Inhacort spacers (Boehringer Ingelheim, Ingelheim, Germany) and Viarox spacer (Byk Gulden, Konstanz, Germany) are devices without a valve. The Nebulator (Astra Pharmaceuticals, Lund, Sweden), Beclomet Spacer (Orion Pharmaceutica, Helsinki, Finland), Volumatic (Glaxo, London, U.K.), Rondo (Klinge Pharma, Munich, Germany), and Fisonair (Fisons, Loughborough, U.K.) all have a kind of 'valve'.

2.2. Aerosols

Two different commercially available cromolyn sodium MDIs were used, aerosols A and B. The aerosol cans were thermostatted in a water-bath at 25°C. Prior to use the aerosol cans were primed by shaking them vigorously for 30 s, waiting 10 s and firing one shot. This procedure was repeated twice. Afterwards, the aerosol can and actuator were cleaned and completely blown dry. For analysis the cans were shaken again for 10 s and after waiting 5 s one shot was released into the apparatus. This was repeated nine times, thus depositing a total of 10 mg of cromolyn sodium into the apparatus.

2.3. Apparatus / assessment of spacers

The Twin Impinger (BP 1988, Appendix XVII C) was used at a continuous air flow of 60 l/min. For each determination 7 ml of water were placed in stage 1 and 30 ml in stage 2. The spacers were attached to the glass throat of the impinger and sealed air tight. The MDIs were fixed to the spacer and also sealed. After firing 10 doses into the apparatus, actuator, spacer, stage 1 and stage 2 were rinsed with water. Stage 1 washings included those from the throat and the stage 1 inlet tube. Stage 2 washings included those from the inside and outside of the stage 2 inlet tube and jet. The washing solutions were then diluted to volume (100 ml) and filtered through a 0.45 μm cellulose nitrate filter. For each spacer, three determinations were performed with each aerosol. Additionally, a control experiment for each aerosol without spacer was carried out (six runs with two aerosol cans each). Confidence intervals of the mean value on a 95% level were calculated to check for statistically significant differences.

2.4. UV determination

The amount of cromolyn sodium in the washing solutions was determined using a Uvikon 930 Spectrophotometer (Kontron Instruments) set at 238.4 nm. The washing solutions had to be diluted up to 10-fold depending on their concentration. The diluted solutions were measured in quartz cuvettes of 1.00 cm length against water. The quantities of drug recovered were calculated as percentages of the total amount found in each experiment.

3. Results and discussion

Results for aerosols A and B are shown in Tables 2 and 3. The fractions of the dose reaching spacer, stage 1 and stage 2 of the impinger are substantially different for the various spacers. The fractions remaining in the actuator did not vary greatly.

Table 2
Percentage of aerosol A deposited in actuator, spacer and stages 1 and 2 of the Twin Impinger

Spacer	Fraction of aerosol A in			
	Actuator	Spacer	Stage 1	Stage 2
Inhacort (telescope)	14.0	29.0	30.4	26.6
Inhacort (normal)	13.4	40.2	20.4	26.0
Viarox	12.4	37.9	22.7	27.0
Aru	13.5	35.7	21.8	29.0
Rondo	11.7	48.6	14.2	25.5
Fisonair	11.9	44.5	19.7	23.9
Nebulator	11.4	66.6	5.2	16.8
Beclomet	11.2	83.6	1.0	4.2
Volumatic	16.1	77.0	2.5	4.4
Without Spacer	15.0	–	55.7	29.3

3.1. Results without spacer

Without spacer, an average of 29.3% of aerosol A ($S = 2.68$) or 18.7% of aerosol B ($S = 1.46$) reach stage 2. With the use of some spacers, however, the respirable fraction of aerosol B not only rises, but in a few cases significantly exceeds the level of aerosol A. This must be due to aerosol formulation. Propellant of aerosol A is a mixture of dichlorodifluoromethane (CFC-12) and dichlorotetrafluoroethane (CFC-114), while aerosol B contains trichlorofluoromethane (CFC-11) additionally. The boiling points of CFC-12 and CFC-114 are −29.8 and 4.1°C, respectively. CFC-11 has a much higher boiling point of 23.7°C and evaporates slowly. This can explain the in-

Table 3
Percentage of aerosol B deposited in actuator, spacer and stages 1 and 2 of the Twin Impinger

Spacer	Fraction of aerosol B in			
	Actuator	Spacer	Stage 1	Stage 2
Inhacort (telescope)	16.6	25.4	21.5	36.5
Inhacort (normal)	19.2	29.2	19.5	32.1
Viarox	19.8	19.3	19.1	41.7
Aru	13.5	37.5	23.8	25.2
Rondo	19.4	35.9	12.0	32.7
Fisonair	18.1	31.8	22.5	27.6
Nebulator	13.7	61.5	3.4	21.4
Beclomet	17.9	74.4	1.0	6.7
Volumatic	17.9	71.9	1.9	8.3
Without Spacer	21.5	–	59.8	18.7

crease in the respirable dose of aerosol B found for some spacers. Formulation aspects, however, shall not be discussed further in this study.

3.2. Spacer performance

Despite these quantitative differences, data for the two aerosols are in agreement. A double sided t-test was made to check for statistically relevant effects of the spacers ($\alpha = 0.05$). The most important parameter is deposition in stage 2, i.e., the 'respirable dose' (see Fig. 1). The data of aerosol A show a group of six spacers (Inhacort spacers, Viarox, Aru, Rondo and Fisonair) that do not significantly change the respirable fraction. These very spacers do increase the respirable fraction of aerosol B to a level around or above aerosol A. This is obviously due to propellant evaporation and demonstrates that spacers may indeed improve respiratory deposition. For the Nebulator, the picture is ambiguous: stage 2 deposition of aerosol A is reduced, while deposition of aerosol B is slightly increased. Two other spacers, Beclomet and Volumatic, reduce stage 2 deposition to a very low level. Possible reasons for this will be discussed later.

Deposition at stage 1 (Fig. 2) significantly decreases for all spacers tested. The extent varies from about 50% reduction to almost zero deposition. This is responsible for the fact that side effects due to extra pulmonary deposition can be reduced by the use of spacers. A useful way to evaluate this reduction is the ratio of the fractions in stage 2 and stage 1 (Table 4). The ratios of the Volumatic and Beclomet are very high. Interpretation is difficult, however, because the output is so low (5–10% of the dose). Of the other spacers, the Nebulator, followed by the Rondo, has the highest ratio. These are most effective in reducing extra pulmonary deposition.

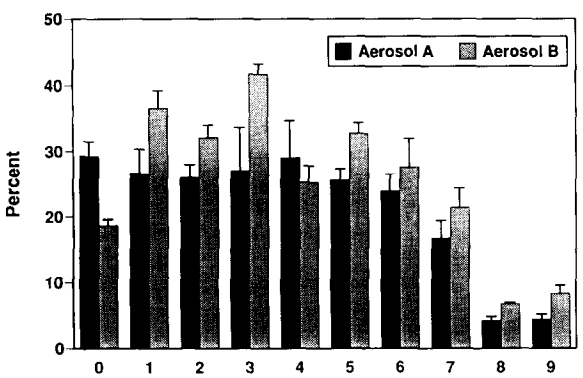

Fig. 1. The effect of different spacers on the respirable fractions ($D_{50\%} < 6.4$ μm) of aerosols A and B. 95% confidence intervals are indicated. 0, control experiment (without spacer); 1, Inhacort (telescope); 2, Inhacort (normal); 3, Viarox; 4, Aru; 5, Rondo; 6, Fisonair; 7, Nebulator; 8, Beclomet; 9, Volumatic.

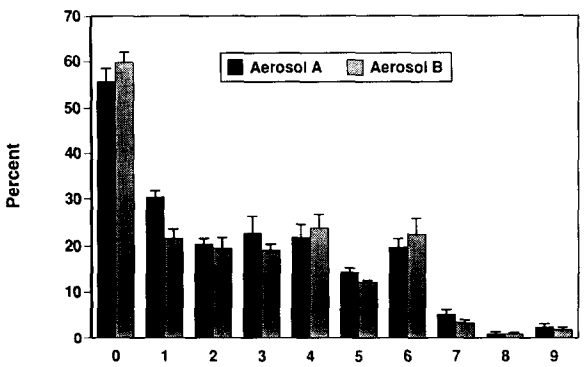

Fig. 2. The influence of different spacers on the non-respirable amount of drug deposited in stage 1 ($D_{50\%} > 6.4$ μm) of the impinger. 95% confidence intervals are indicated. 0, control experiment (without spacer); 1, Inhacort (telescope); 2, Inhacort (normal); 3, Viarox; 4, Aru; 5, Rondo; 6, Fisonair; 7, Nebulator; 8, Beclomet; 9, Volumatic.

Table 4
Ratio of fractions in stage 2 and 1; the higher the ratio the more effectively reduced is deposition in stage 1

Spacer	Ratio aerosol A	Ratio aerosol B
Inhacort (telescope)	0.88	1.70
Inhacort (normal)	1.27	1.65
Viarox	1.19	2.18
Aru	1.33	1.06
Rondo	1.80	2.73
Fisonair	1.21	1.23
Nebulator	3.23	6.29
Beclomet	4.20	6.70
Volumatic	1.76	4.37
Without Spacer	0.53	0.31

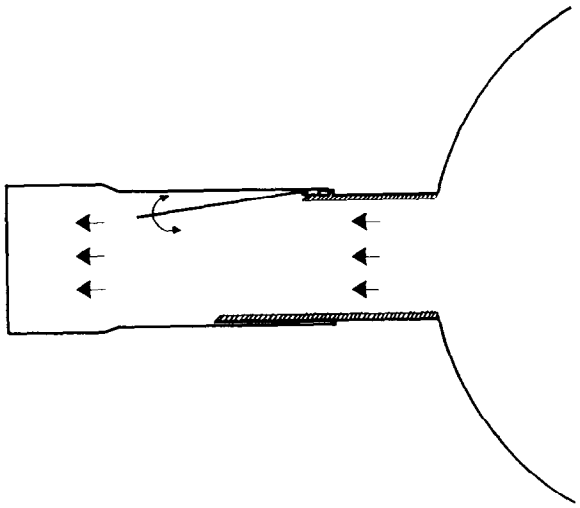

Fig. 3. The valve in the Rondo spacer: when air is inhaled through the device, the plastic flaps flip upwards and aerosol particles can pass through.

Deposition in the spacer device itself is generally high. Approx. 20–85% of the drug is recovered there. It is not possible to correlate spacer volume with deposition in the spacer and/or deposition in stage 2.

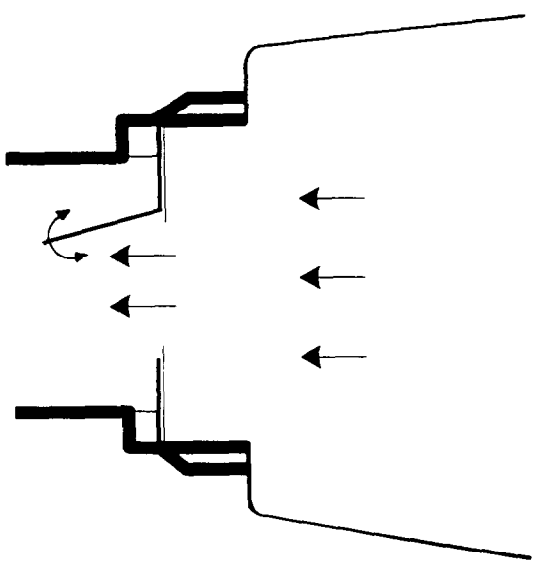

Fig. 4. The valve in the Fisonair spacer. The rubber membrane is bent aside and opened by the air stream.

3.3. Spacer construction

The spacers differ in their construction and valve systems (see Table 1): four spacers, the two Inhacort spacers, Viarox and Aru spacer, are very simple devices without a valve. They strongly reduce stage 1 deposition and may even enhance stage 2 deposition. The aerosol cloud is not blocked on its way out of the device. The other spacers tested have various kinds of built in valves. These serve to keep particles from flying straight through the device. Stage 1 deposition is diminished even more but stage 2 deposition may also be affected.

In the ball-shaped Rondo spacer, the MDI is actuated from the side. Thus, larger particles impact on the spacer wall and do not even reach the valve. The valve itself is a small plastic flap (Fig. 3) that is easily moved aside by the inhalative air flow. Therefore, stage 2 deposition is high. The Fisonair spacer has a small rubber membrane at its exit (Fig. 4). This membrane will

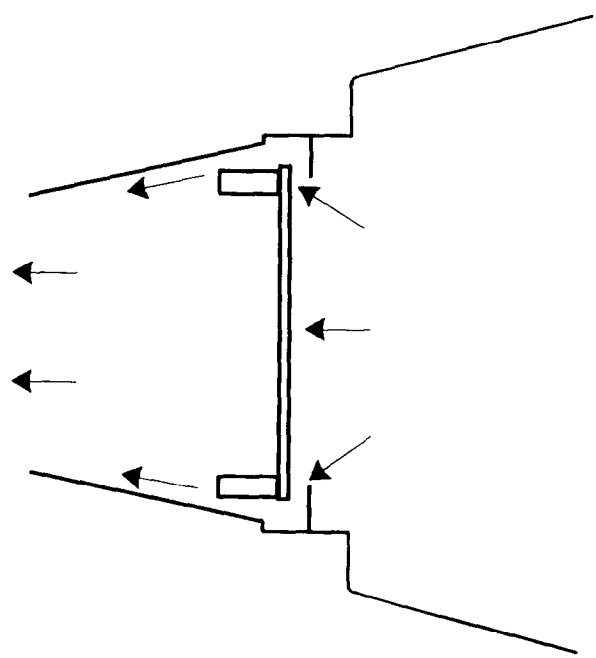

Fig. 5. The valve in the Volumatic spacer (similar in the Beclomet spacer): During inhalation, the plate is pushed forward. A high percentage of particles impacts on the flat plate that is placed perpendicularly to the air stream.

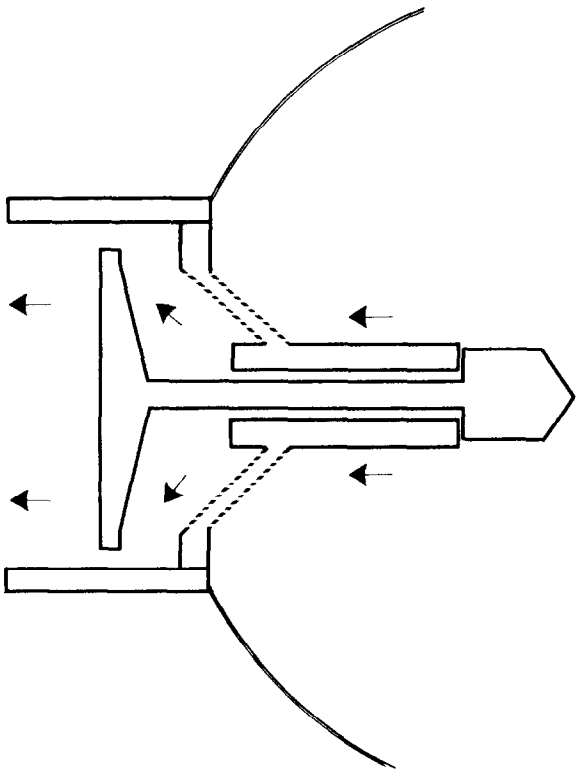

Fig. 6. The valve in the Nebulator spacer. The end of the plug is conical in form, deflecting the air stream to the side. Thus, particles are led around the plug and do not impact as much as in the Volumatic and Beclomet spacer.

be bent away as air flows through the device. Particle transport is not severely handicapped. Three spacers, the Nebulator, Beclomet and Volumatic, have a more sophisticated valve system. A trapdoor-like lid is built into the spacer exit. This must be pushed forward by the air stream in order to be opened. The lid of the Nebulator and Volumatic is flat and placed perpendicularly to the air stream (Fig. 5). It is similar to an impaction plate in a cascade impactor. Obviously, most particles impact on this plate and only the smallest are able to go around it. We suppose this is the explanation as to why the output of these spacers is so low. In the Nebulator spacer, the lid has a convex form (Fig. 6). Thus, the change in direction is less sudden. The air stream is more readily deflected to the side and particles impact to a lesser extent. Particle output is higher.

All in all, the spacer devices tested cannot be called equivalent. The differences observed seem to be mainly due to construction of the valve. It is not possible to show a correlation of spacer shape and size with the respirable output. Stage 1 deposition accounts for deposition outside the lower respiratory tract and may result in local or systemic side effects in vivo. This fraction is markedly reduced with all spacers. The most effective reduction occurs with the Nebulator and Rondo. The respirable fraction (stage 2) deposition is highest with the Inhacort, Viarox, Aru, Rondo and Fisonair spacers.

4. References

British Pharmacopoeia, 1988, Appendix XVII-C, Pressurised inhalations: deposition of the emitted dose. HM Stationery Office, London, A204–A207.

Brown, P.H., Blundell, G., Greening, A.P. and Crompton, G.K., Do large spacer devices reduce the systemic effects of high dose inhaled corticosteroids? *Thorax*, 45 (1990) 736–739.

Byron, P.R., *Respiratory Drug Delivery*, CRC Press, Boca Raton, FL, 1990, p. 173.

Crompton, C.G., Problems patients have using pressurized aerosol inhalers. *Eur. J. Respir. Dis.*, 63 (1982) 101–10.

Gayrard, P. and Orehek, J., Mauvaise utilisation des aerosol-doseurs par les asthmatiques. *Respiration*, 40 (1980) 47–52.

Hallworth, G.W. and Westmoreland, D.G., The Twin Impinger: A simple device for assessing the delivery of drugs from metered dose pressurized inhalers. *J. Pharm. Pharmacol.*, 39 (1987) 966–972.

König, P., Spacer devices used with metered-dose inhalers. *Chest*, 88 (1985) 276–284.

Martonen, T.B., Katz, I., Fults, K. and Hickey, A.J., Use of analytically defined estimates of aerosol respirable fraction to predict lung deposition patterns. *Pharm. Res.*, 9 (1992) 1634–1639.

Moren, F., Drug deposition of pressurized inhalation aerosols I. Influence of actuator tube design. *Int. J. Pharm.*, 1 (1978) 205–212.

Moren, F. and Andersson, J., Fraction of the dose exhaled after administration of pressurized inhalation aerosols. *Int J. Pharm.*, 6 (1980) 295–300.

Newman, S.P., Clinical and experimental aspects. In Clarke, S.W. and Pavia, D. (Eds), *Aerosols and the Lung*, Butterworths, London, 1985, pp. 197–224.

Newman, S.P., Clark, A.R., Talaee, N. and Clarke, S.W., Pressurized aerosol deposition in the human lung with and without an 'open spacer' device. *Thorax*, 44 (1989) 706–710.

Newman, S.P., Millar, A.B., Lennard-Jones, T.R., Moren, F. and Clarke, S.W., Improvement of pressurized aerosol deposition with the nebuhaler spacer device. *Thorax*, 39:935–941(1984).

Newman, S.P., Moren, F., Pavia, D., Little, F. and Clarke, S.W., Deposition of pressurized suspension aerosols inhaled through extension devices. *Am. Rev. Respir. Dis.*, 124 (1981b) 317–320.

Newman, S.P., Pavia, D., Moren, F., Sheahan, N.F. and Clarke, S.W., Deposition of pressurized aerosols in the human respiratory tract. *Thorax*, 36 (1981a) 52–55.

Phillips, E.M., Byron, P.R., Fults, K. and Hickey, A.J., Optimized inhalation aerosols: II. Inertial testing methods for particle size analysis of pressurized inhalers. *Pharm. Res.*, 7 (1990) 1228–1233.

Rance, R.W., Studies of the factors controlling the action of hair sprays: III. The influence of particle velocity and diameter on the capture of particles by arrays of hair fibers. *J. Soc. Cosmet. Chem.*, 25 (1974) 545–561.

Vidgren, M.T., Paronen, T.P., Kärkkäinen, A. and Karjalainen, P., Effect of extension devices on the drug deposition from inhalation aerosols. *Int. J. Pharm.*, 39 (1987) 107–112.