*International Journal of Pharmaceutics*, 1 (1978) 213–218



# DRUG DEPOSITION OF PRESSURIZED INHALATION AEROSOLS II. INFLUENCE OF VAPOUR PRESSURE AND METERED VOLUME

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(Received January 13th, 1978)
(Accepted February 1st, 1978)

## SUMMARY

The influence of vapour pressure and metered dose volume on drug deposition was tested using terbutaline sulphate pressurized aerosols with the conventional Bricanyl actuator and an attached tube. In each test the nine healthy volunteers inhaled eight doses at 1 min intervals coordinated with the dose firing. The amount of drug deposited in actuator, tube and mouth was determined spectrophotometrically. It was found that the increase in vapour pressure from 374 kPa to 502 kPa resulted in a significantly higher deposition of drug in the actuator but in a significantly lower deposition in the tube, in the mouth and for the net total loss in actuator, tube and mouth. An increase in metering volume from 25 or 50 μl to 100 μl resulted in a significantly higher deposition of drug in the actuator, in the tube and for the net total loss in actuator, tube and mouth. In order to obtain a high availability of drug to the airways the metering volume of the pressurized aerosol should be low and the vapour pressure high.

## INTRODUCTION

In an earlier study (Morén, 1978) it was shown that the deposition of drug in the mouth could be reduced significantly as the distance from the actuator orifice to the mouth was increased by attaching a tube to the aerosol actuator. The total loss of drug substance in actuator, tube and mouth could also be reduced significantly indicating the possibility of increasing availability of the drug to the airways. The results were probably due to a more complete evaporation of the propellants and a reduced droplet velocity before the aerosol droplets reached the mouth. A reduced droplet size cannot only be obtained by an increase in time for improved evaporation, but also by a higher vapour pressure of the propellant mixture (Wiener, 1958). Furthermore, it is probable that the release of a high volume of propellants at each actuation will retard the evaporation from

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the aerosol droplets compared to the release of a low volume as the evaporation of the propellants is dependent on the fact that energy is acquired from the surrounding atmosphere. In the present study the influence of vapour pressure and metered dose volume on drug deposition was tested on healthy volunteers using terbutaline sulphate pressurized aerosols with the conventional actuator and an attached tube.

## MATERIALS AND METHODS

In all tests the conventional oral actuator, Bricanyl, AB Draco, Sweden, was used in combination with a long glass tube (100 mm length; 32 mm inner diameter) (Fig. 1). Pressurized aerosols were formulated to release the same amount of micronized terbutaline sulphate, 0.25 mg, at each actuation but in various metering volumes: 25, 50 and 100 μl. The concentration of the non-volatile surfactant sorbitan trioleate was the same in all formulations. Propellant mixtures were chosen to give a medium vapour pressure, 374 kPa, and a high vapour pressure, 502 kPa, at 20°C. The vapour pressures were calculated according to Sanders (1970). For detailed formulations see Table 1.

Nine healthy volunteers were trained to fire an aerosol in the beginning of a deep inhalation. The volunteers were then tested with each of the six various formulations in a random order. On each occasion eight doses were administered with an interval of 1 min between each dose. The performance and analyses were made according to Morén (1978).

Each volunteer kept the same actuator and tube throughout the tests. The mean dose delivery by the valve was 0.235 (S.D. ± 0.017) mg of terbutaline sulphate determined before the start and at the end of the tests for the aerosols used. The metering volume was determined for the individual aerosols by weight loss after five actuations. The metering volume for the individual aerosols did not deviate from the nominal metering volumes by more than 7.0% at the start or at the end of the tests. As the aerosols were provided with metering valves it was not possible to determine the vapour pressures accurately for the aerosols used in the tests.

A statistical analysis was separately performed on each of the four following variables: terbutaline sulphate in actuator, terbutaline sulphate in tube, terbutaline sulphate in

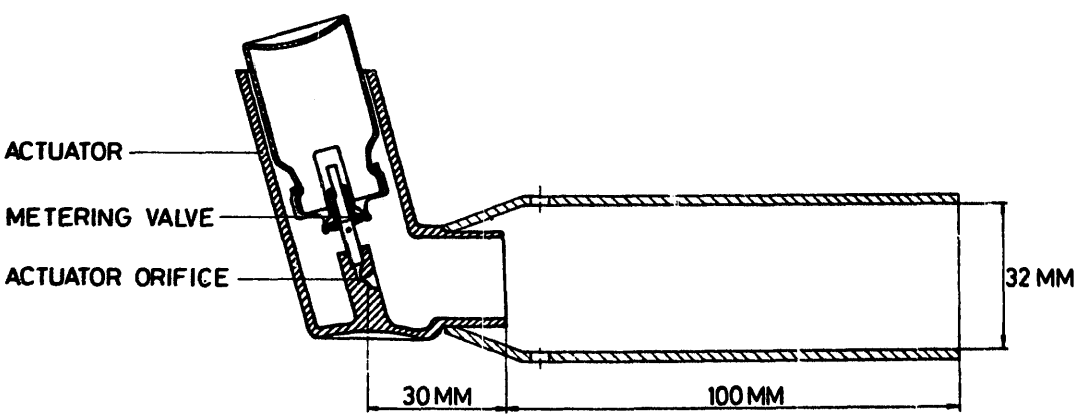


Fig. 1. Actuator combined with tube of 100 mm length and 32 mm inner diameter.

TABLE 1

COMPOSITION, VAPOUR PRESSURE AND METERING VOLUME OF PRESSURIZED AEROSOLS

| | A | B | C | D | E | F |
|---|---|---|---|---|---|---|
| Terbutaline sulphate, mg/ml | 10 | 5 | 2.5 | 10 | 5 | 2.5 |
| Sorbitan trioleate, mg/ml | 14 | 14 | 14 | 14 | 14 | 14 |
| Trichlorofluoromethane (propellant 11), mg/ml | 344 | 345 | 346 | 206 | 207 | 208 |
| Dichlorotetrafluoroethane (propellant 114), mg/ml | 344 | 345 | 346 | 0 | 0 | 0 |
| Dichlorodifluoromethane (propellant 12), mg/ml | 688 | 691 | 692 | 1170 | 1174 | 1176 |
| Vapour pressure at 20°C, kPa | 374 | 374 | 374 | 502 | 502 | 502 |
| Metering volume, µl | 25 | 50 | 100 | 25 | 50 | 100 |

mouth, and total loss (sum of terbutaline sulphate in actuator, tube and mouth). The analysis was made according to the model for a randomized block design with persons as the block factor. The factor studied was six different combinations of vapour pressures and metering volumes. In the analysis of variance the effect of treatment was divided into one main effect for vapour pressure, one main effect for metering volume, and the interaction between vapour pressure and metering volume.

## RESULTS

The proportions of terbutaline sulphate found in actuator, tube and mouth as well as total loss (sum of amounts in actuator, tube and mouth) are presented in Table 2 and the

TABLE 2

PER CENT OF THE DELIVERED TERBUTALINE SULPHATE DOSE FOUND IN ACTUATOR, TUBE AND MOUTH

Mean values from nine volunteers, and residual standard deviations (df = 40) from the analyses of variance

| Formulation | Per cent deposited | | | |
|---|---|---|---|---|
| | Actuator | Tube | Mouth | Sum |
| A. 25 µl; 374 kPa | 6.8 | 23.6 | 12.7 | 43.1 |
| B. 50 µl; 374 kPa | 6.2 | 24.1 | 13.7 | 44.1 |
| C. 100 µl, 374 kPa | 8.0 | 29.7 | 14.2 | 51.9 |
| D. 25 µl; 502 kPa | 7.4 | 18.0 | 8.3 | 33.7 |
| E. 50 µl; 502 kPa | 7.9 | 22.8 | 11.3 | 42.1 |
| F. 100 µl; 502 kPa | 10.7 | 25 1 | 10.1 | 45.9 |
| Residual standard deviation | 1.36 | 2.83 | 3.00 | 3.74 |

TABLE 3

DEPOSITION OF TERBUTALINE SULPHATE IN THE ACTUATOR. ANALYSIS OF VARIANCE

df = degrees of freedom; SS = sum of squares; MS = mean square; $F$ = variance ratio.

| Factor | df | SS | MS | $F$ |
|---|---|---|---|---|
| Individuals | 8 | 55.71 | 6.96 | |
| Treatments | 5 | 107.77 | 21.55 | 11.69 [a] |
| pressures | 1 | 36.29 | 36.29 | 19.68 [a] |
| volumes | 2 | 61.35 | 30.68 | 16.64 [a] |
| pressures X volumes | 2 | 10.13 | 5.06 | 2.75 NS |
| Individuals X treatments | 40 | 73.75 | 1.84 | |

[a] $P < 0.001$; NS, not significant ($P > 0.05$).

TABLE 4

DEPOSITION OF TERBUTALINE SULPHATE IN THE TUBE. ANALYSIS OF VARIANCE

df = degrees of freedom; SS = sum of squares; MS = mean square; $F$ = variance ratio.

| Factor | df | SS | MS | $F$ |
|---|---|---|---|---|
| Individuals | 8 | 320.77 | 40.10 | |
| Treatments | 5 | 635.44 | 127.09 | 15.89 [a] |
| pressures | 1 | 197.76 | 197.76 | 24.73 [a] |
| volumes | 2 | 392.57 | 196.29 | 24.55 [a] |
| pressures X volumes | 2 | 45.10 | 22.55 | 2.82 NS |
| Individuals X treatments | 40 | 319.84 | 8.00 | |

[a] $P < 0.001$; not significant ($P > 0.05$).

TABLE 5

DEPOSITION OF TERBUTALINE SULPHATE IN THE MOUTH. ANALYSIS OF VARIANCE

df = degrees of freedom; SS = sum of squares; MS = mean square; $F$ = variance ratio.

| Factor | df | SS | MS | $F$ |
|---|---|---|---|---|
| Individuals | 8 | 3208.29 | 401.04 | |
| Treatments | 5 | 233.46 | 46.69 | 5.18 [a] |
| pressures | 1 | 179.71 | 179.91 | 19.92 [a] |
| volumes | 2 | 43.21 | 21.60 | 2.39 NS |
| pressures X volumes | 2 | 10.55 | 5.28 | 0.58 NS |
| Individuals X treatments | 40 | 360.84 | 9.02 | |

[a] $P < 0.001$; NS, not significant ($P > 0.05$).

TABLE 6

TOTAL LOSS OF TERBUTALINE SULPHATE. ANALYSIS OF VARIANCE

df = degrees of freedom; SS = sum of squares; MS = mean square; $F$ = variance ratio.

| Factor | df | SS | MS | $F$ |
|---|---|---|---|---|
| Individuals | 8 | 3426.57 | 428.32 | |
| Treatments | 5 | 1573.53 | 314.71 | 22.45 [a] |
| pressures | 1 | 459.03 | 459.03 | 32.75 [a] |
| volumes | 2 | 991.33 | 495.67 | 35.37 [a] |
| pressures X volumes | 2 | 123.16 | 61.58 | 4.39 [b] |
| Individuals X treatments | 40 | 560.61 | 14.02 | |

[a] $P < 0.001$.
[b] $P < 0.05$.

analyses of variance in Tables 3–6. The increase of vapour pressure from 374 to 502 kPa resulted in a significantly ($P < 0.001$) higher deposition of terbutaline sulphate in the actuator but in a significantly ($P < 0.001$) lower deposition in the tube, in the mouth and for the total loss. The metering volume effect was significant ($P < 0.001$) for deposition of terbutaline sulphate in the actuator and the tube as well as for the total loss. For these three variables higher volumes resulted in higher deposition, with the single exception that no clear difference was observed for the actuator between the two lower volumes. The metering volume effect was not significant for deposition in the mouth. The interaction between vapour pressure and metering volume was found to be significant ($P < 0.05$) for the total loss of terbutaline sulphate but not significant for deposition in the actuator, in the tube or in the mouth.

## DISCUSSION

In the present study all tests were made with a long tube attached to the conventional actuator. The design with a tube was chosen in order to minimize variation of the deposition in the mouth compared to the use of the actuator alone. The aerosol droplets expelled from the actuator orifice have a high velocity close to the orifice but are decelerated by air resistance (Wiener, 1958). An increase in vapour pressure results in higher initial velocity of the droplets but also in smaller initial droplets and more rapid propellant evaporation. The impaction of aerosol droplets is increased by raising their velocity but decreased by smaller droplet size (Lippmann and Albert, 1969). The increase in vapour pressure from 374 to 502 kPa resulted in a higher deposition of drug substance in the actuator. This was probably dependent on the influence of an increased initial velocity of the aerosol droplets. On the other hand, the increase in vapour pressure resulted in a lower deposition of drug in the tube and the mouth probably dependent on greater influence of the reduction in droplet size and less influence of the velocity of the droplets as the droplets were decelerated. The total loss of terbutaline sulphate in the actuator, tube and mouth could be reduced significantly by increasing the vapour pressure. Thus the increased deposition in the actuator was compensated by considerably less

deposition in the tube and in the mouth. The vapour pressure of 374 kPa in formulations A, B and C was increased to 502 kPa by eliminating the content of propellant 114 and reducing the content of propellant 11. The presence of propellant 11 was necessary in order to allow the preparation of the drug suspension concentrate at room temperature when manufacturing the pressurized aerosols. The content of the surfactant sorbitan trioleate in the pressurized aerosols was necessary for the physical stability of the micronized drug suspension and for lubrication of the metal valve. As soluble non-volatile components retard the flashing and evaporation of the propellants (Wiener, 1958), the concentration of sorbitan trioleate was kept at the same level in all formulations.

When the aerosol droplets pass through the air, energy is acquired from the surrounding atmosphere for further evaporation of the propellants. However, as the metering volume increases there is a higher quantity of propellants to be evaporated by the limited surrounding space. The increase of the metering volume from 25 or 50 $\mu$l to 100 $\mu$l resulted in an increased deposition of drug substance in the actuator, in the tube and for the total loss. This probably depends on a retarded evaporation of the propellants.

The present investigation has shown that the deposition of drug substance from pressurized inhalation aerosols can be influenced both by vapour pressure and metering volume. In order to obtain a low total deposition of drug substance in the actuator, tube and mouth, indicating a high availability to the airways, the metering volume of the pressurized aerosol should be low and the vapour pressure high. For pressurized inhalation aerosols the metering volumes used are normally within the range of 25–100 $\mu$l. For lower metering volumes it is difficult to obtain the necessary precision for accuracy of dose volume. Considering the use of a high vapour pressure it should be noted that the seal of the valve must be efficient so that the leakage of propellants is not higher than acceptable limits (National Formulary, 1975).

ACKNOWLEDGEMENT

I am grateful to Dr. C.J. Lamm who performed the statistical analysis.

REFERENCES

Lippmann, M. and Albert, R.E., The effect of particle size on the regional deposition of inhaled aerosols in the human respiratory tract. Am. Ind. Hyg. Assoc. J., 30 (1969) 257–275.

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

National Formulary XIV, (1975) 849.

Sanders, P.A., Principles of Aerosol Technology, Van Nostrand Reinhold, New York, 1970, Ch. 9.

Wiener, M.V., How to formulate aerosols to obtain the desired pattern. J. Soc. Cosmet. Chem., 9 (1958) 289–297.