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IN VITRO DOSE SAMPLING FROM PRESSURIZED INHALATION AEROSOLS. INVESTIGATON OF PROCEDURES IN BPC AND NF

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SUMMARY

In the British Pharmaceutical Codex and National Formulary, pressurized inhalation aerosols are assayed with regard to the dose available to the patient. The tests involve a correction for loss of drug substance in the inhalation device. In the present study, the in vitro procedures were investigated for appropriate sampling. A high drug retention was found in the valve stem. This retention decreased at short intervals between actuations. Drug retention in the actuator increased when the recipient volume of air was small and the air flow rate was low. The results indicate that sampling from pressurized inhalation aerosols should be made into the air at a fixed interval between actuations. It is also recommended that the flow rate is increased compared with the National Formulary monographs.

INTRODUCTION

Pressurized aerosols for oral inhalation are used for drug administration into the lower respiratory tract mostly to obtain a local activity. This gives the advantages of a rapid onset of action and a low degree of systemic side-effects. Local side-effects might occur, however, in the oral cavity as a result of high local concentration after deposition of the drug substance (Clark et al., 1975). A great part of the dose available to the patient is swallowed into the gastrointestinal tract both after deposition in the oral cavity and after mucociliary clearance (Walker et al., 1972; Nillson et al., 1976). Some aerosol particles are exhaled as they are not deposited during the respiratory cycle. The deposition of aerosol particles is dependent not only on such variables as particle velocity, aerodynamic diameter and potential changes of it, but also on breathing pattern and diseased states of the respiratory tract (Task Group on Lung Dynamics, 1966; Gorman and Hall, 1973). The site of action after oral inhalation is not well established, but it can be assumed that

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the drug substance must be able to reach the lower respiratory tract in order to exert local activity. The same assumption can be made for systemic activity through local absorption from the lower respiratory tract. Systemic activity is occasionally utilized after oral inhalation.

Pressurized aerosols are also used by nasal inhalation for local activity in the nasal cavity. This administration requires a high local deposition as the fraction of drug substance inhaled into the lower respiratory tract will not be useful for the intended activity.

As a pressurized inhalation aerosol is actuated, some drug substance is retained in the inhalation device. Thus the amount available to the patient is less than the dose released. It was shown that the use of an additional tube connected to an oral actuator reduced the dose available to the patient but decreased the deposition in the oral cavity so that the resulting dose available for possible local activity increased (Morén, 1978a). A lower metering volume or a change in formulation to a higher vapour pressure gave a similar result (Morén, 1978b). In the British Pharmaceutical Codex (BPC; 1973) it is required that the label for pressurized inhalation aerosols should state the amount of drug substance available to the patient. For both oral and nasal inhalation aerosols this is determined by subtracting the amount retained in the actuator from the amount delivered by the valve. To determine the latter amount, the assembled unit is immersed into an absorbing solution and a number of doses are released. The drug substance retained in the actuator is determined after actuations into the free air.

In the National Formulary (NF; 1975) only aerosols for oral inhalation are covered. A unit spray sampling apparatus is used to obtain a sample from the assembled container and actuator. The sampling apparatus consists of an intake tube measuring approximately 5 X 15 cm, a delivery tube to which is attached a sintered-glass dispersion bubbler and a collection chamber containing an absorbing solution. Some modifications of the NF sampling apparatus are permitted. To avoid loss of drug substance into the atmosphere, air is continuously drawn through the apparatus at a rate of 12 ± 1 litres $\cdot$ min^{-1}. This is much lower than the maximum inspiratory flow rate obtained by patients. Coady et al. (1976) found that for a random selection of 30 asthmatics 50–400 litres $\cdot$ min^{-1} was reached.

The aim of the present study was to investigate these sampling procedures with respect to doses from pressurized inhalation aerosols that are described in BPC and NF. From ealier tests on volunteers (Morén, 1978a), it was evident that the retention of drug substance in the actuator was dependent on the air flow rate and the recipient volume of air. In this study we investigated the influence of these two factors as well as possible retention of drug substance in the valve stem.

MATERIALS AND METHODS

A pressurized inhalation aerosol with a nominal dose of 0.25 mg terbutaline sulphate released by the valve was used in the tests together with its oral actuator (Bricanyl, AB Draco, Sweden). The details of the metering valve are described in Fig. 1. The stainless steel stem was blind in the upper end but open in the lower end. At actuation, the metered volume was released through the stem opening into the actuator seat. The retention of drug substance in the valve stem was determined in 10 separate assays after the

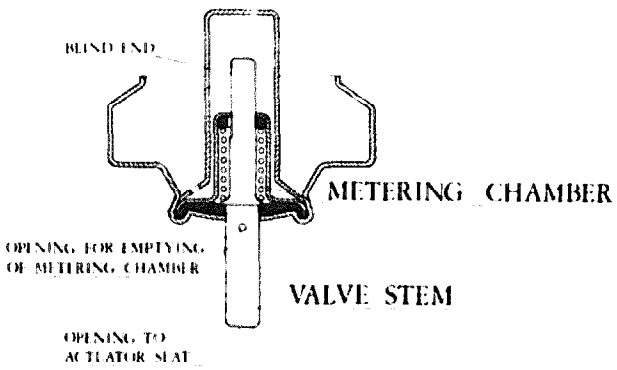

Fig. 1. Details of metering valve.

release of 10 doses. The actuations were made by means of one dose ever 1 s, or every 5 s, 60 s, or 12 h. The container was shaken between the actuations except at the short interval of 1 s.

For testing of retention in the actuator, 10 doses were released into the air with one dose every 5 s. The actuator was directed either into the free air (as in the BPC procedure), into a box measuring 30 X 30 X 50 cm, or into an intake tube in the NF unit spray sampling apparatus. The volume of the box was intended to be so large that the release of a dose through the actuator could be considered comparable to actuation into the free air. Air could be drawn through a small tube placed opposite the inserted actuator, 50 cm away from it. The NF intake tube either had the dimensions stated above or was modified to the smaller dimensions of 4 X 8 cm known to be used by some laboratories. The air flow through the box or the NF tubes was arranged by a vacuum pump and the rate was controlled with a flowmeter to zero, 2.50×10^{-4} m$^3 \cdot$ s^{-1} (15 litres $\cdot$ min^{-1}) or 6.67×10^{-4} m$^3 \cdot$ s^{-1} (40 litres $\cdot$ min^{-1}). In the tests the same 9 actuators were used as in the previous tests on volunteers. In a separate test 9 additional actuators were used. The seats for the valve stem were cut out from these actuators. For determination of drug retention in this part of the actuator, 10 doses were released into the free air through the isolated seat with one dose every 5 s.

For estimation of the efficiency of the collection chamber in the NF sampling apparatus, the retention on a glass fibre filter (Whatman GF/A) was determined in 10 separate assays. The filter was located between the collection chamber and the vacuum system. Earlier, Bell et al. (1973) showed that this type of filter produced a quantitative recovery for pressurized inhalation aerosols when used in a multistage liquid impinger.

In order to determine the amount of terbutaline sulphate retained in the valve stem, actuator, or actuator seat, these were washed with ethanol–water 50 : 50 and the solutions were spectrophotometrically assayed after reaction with 4-aminoantipyrine and potassium ferricyanide at pH 9.5 (Morén,1978a). The amount on the filter was determined in the aqueous phase after shaking with 15 ml of 0.003 mol $\cdot$ litre^{-1} sulphuric acid and 15 ml of chloroform. The percentage retention of terbutaline sulphate was based on the dose delivered by the valve for each aerosol. The mean dose delivered by the valve was 0.218 (S.D. = 0.010) mg of terbutaline sulphate for the 17 aerosol containers used in the tests determined according to Morén (1978a).

As the same actuators were used in all studies on the complete units, statistical comparisons were made by means of paired *t*-test.

RESULTS

Valve stem

A high retention of drug substance was found in the stem after releasing doses through the actuator into the free air, see Table 1. The retention was lower when intervals between actuations were brief. Retention of drug substance in the valve stem was partly dependent on a passage into the blind end. When the intervals between actuations were brief, unevaporated propellants probably filled the blind end so that a lower amount of drug was deposited. A moulded plastic stem with a compact upper end was used in a separate test and it was confirmed that such a stem gave less retention, 4.5% (S.D. = 0.8) at the 60-s interval.

Actuator

Deposition in the actuator is presented in Table 2. At the flow rate zero or 2.50×10^{-4} $m^3 \cdot s^{-1}$ through the actuator we found a significantly higher deposition for the actuator connected to the intake tubes of the NF sampling apparatus compared with actuations into the free air ($P < 0.001$). At the highest flow rate we only found a small but significant difference between the NF tube 4 × 8 cm and actuations into the free air ($P < 0.05$). The deposition was significantly higher in the small NF tube at the flow rate zero or 2.50×10^{-4} $m^3 \cdot s^{-1}$ ($P < 0.01$ and $P < 0.05$, respectively), so the tubes were not equivalent. The volume of the box was sufficient to give about the same retention in the actuator as when actuations were made into the free air. The retention was reduced when air was drawn through the box. At the flow rate 6.67×10^{-4} $m^3 \cdot s^{-1}$ it was very similar to the retention in the isolated seats for which we found 3.7% (S.D. = 0.8). The actuator deposition increased when the recipient volume was small. This seemed to be compensated by an air flow through the actuator. At the highest flow rate and a large recipient volume, drug deposition probably occurred in the actuator seat only.

TABLE 1

DRUG DEPOSITION IN VALVE STEM AT DIFFERENT INTERVALS BETWEEN ACTUATIONS

Ten doses actuated into the free air. Mean values and S.D. from 10 assays.

Interval between actuations	Per cent deposited	
1 s	4.7 ± 0.5	} a
5 s	10.9 ± 1.4	} a
60 s	18.2 ± 2.5	} N.S.
12 h	17.1 ± 3.9	

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

TABLE 2

DRUG DEPOSITION IN ACTUATOR USING DIFFERENT RECIPIENTS AND FLOW RATES

Per cent of the delivered terbutaline sulphate dose found in actuator after releasing 10 doses at the interval of 5 s. Mean values and S.D. from 9 actuators.

Recipient	Per cent deposited		
	Flow rate ($m^3 \cdot s^{-1}$)		
	0	2.50×10^{-4}	6.67×10^{-4}
Free air	7.6 ± 0.5	–	–
NF tube 4 × 8 cm	41.6 ± 4.6	13.1 ± 3.1	6.5 ± 1.0
NF tube 5 × 15 cm	31.1 ± 6.3	10.3 ± 1.6	6.7 ± 2.1
Box 30 × 30 × 50 cm	7.3 ± 0.6	4.8 ± 0.5	3.6 ± 0.6

Absorbing solution

The loss of drug substance with air leaving the NF sampling apparatus could be neglected, as it was determined to be less than 0.4%. A similar determination was difficult to perform concerning the loss in the BPC method as regards the amount delivered by the valve. It is likely that some drug substance is lost due to the short distance for the bubbles containing aerosol particles to pass through the layer of absorbing solution.

DISCUSSION

Pressurized inhalation aerosols are sometimes labelled with the dose available to the patient according to BPC and NF, but sometimes the nominal dose released by the valve is used. The present inconsistency in labelling involves a confusion that could be eliminated by using the same system for all products. Neither the dose available to the patient nor the nominal dose gives satisfactory characterization of the availability at the intended site of action in the respiratory tract. The bioavailability is dependent on such variables as formation of the contents, physicochemical nature and aerodynamic diameter of the aerosol particles, metering volume, valve design and actuator design, but also on the route of administration, breathing pattern and the patient's particle clearance and diseased states of the respiratory tract. Although it will not be practicable to cover all these parameters in one in vitro model, the main parameters could possibly be covered in a satisfactory model for both oral and nasal pressurized inhalation aerosols. As long as such a model is not available, the required tests concerning the dose delivered to the patient in BPC and NF should be performed in a way that reflects the use in vivo.

In the study, a high retention of drug substance was found in the valve stem as actuations were made into the air. This indicates that the in vitro sampling should be performed into the air according to the use of the inhalation aerosol by the patient, and not into a liquid as in the BPC test concerning the amount delivered by the valve, where the drug substance is washed out of the stem. In the BPC method the drug deposited in the

valve stem will erroneously be determined as available to the patient. In the tests, drug retention in the valve stem varied at different intervals between actuations. The use of a fixed interval should be stated in the methods. The minimum interval needed to reflect the use in vivo is probably dependent both on formulation and on valve design.

The results indicate that the flow rate in the NF sampling apparatus should be increased to about 6.67×10^{-4} $m^3 \cdot s^{-1}$. Drug retention in the actuator is then comparable with the results from volunteers (Morén, 1978a). The determination of drug retention in the actuator described in BPC by releasing doses through the actuator into the free air seems to give results comparable to those obtained in vivo. Thus, the procedure can be used for the determination of actuator retention, for instance in the control of the moulding process of the actuator.

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