International Journal of Pharmaceutics, 5 (1980) 287–290

INVESTIGATION OF ASSAY PROCEDURES FOR PRESSURIZED INHALATION AEROSOLS

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(Received March 28th, 1980)
(Accepted April 1st, 1980)

SUMMARY

In compendial procedures the concentration in pressurized inhalation aerosols is determined after actuation into a reception liquid contained in a pressure tube or after actuation under the surface of a reception liquid contained in a beaker. In the present study, the recovery of these sampling procedures was investigated and compared with a determination based on the total drug content in the same aerosol units. The sampling procedure involving actuation into a pressure tube was found to be incomplete mainly because of drug retention in the valve stem. The results indicate that a correction should be made for the valve stem retention. Actuation under the surface of chloroform resulted in a low recovery, as some drug substance was probably lost into the air.

INTRODUCTION

A pressurized inhalation aerosol consists of a solution or a suspension of drug substance in a liquid propellant mixture. The container is sealed by means of a metering valve. When a dose is actuated, a metered volume of the contents is released through the valve stem. The container is usually filled with a volume corresponding to a number of doses in the range of 200–400. One important aspect of the production control is to determine the concentration of drug substance in the formulation. The British Pharmaceutical Codex (BPC; 1979) requires that the label on pressurized inhalation aerosols should state the concentration of active ingredient, but no sampling procedure is indicated. Young et al. (1960) described the assay of a suspension aerosol after a partial evaporation of the propellants and the collection of the drug particles on a glass sinter filter. Tuesley et al. (1968) suggested the sampling of metered doses into a pressure chamber for determination of the drug concentration in pressurized aerosols. National Formulary XIV

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(NF XIV; 1975) describes an apparatus for sampling the contents of aerosol containers provided with metering valves. The sampling apparatus consists of a pressure tube containing a reception liquid and fitted with a firing adapter. No correction is made for drug retention in the valve stem which may occur to a variable extent (Morén and Jacobsson, 1979). The container sampling apparatus has been deleted in the United States Pharmacopeia XX – National Formulary XV (USP XX-NF XV; 1980). The individual aerosol monographs specify another procedure in which the dose is actuated under the surface of chloroform in a beaker. After actuation the valve stem is rinsed with chloroform, and the rinsings are collected with the sample in the beaker.

The aim of the present study was to investigate the recovery in the two sampling procedures according to NF XIV and USP XX-NF XV for the assay of pressurized inhalation aerosols. Comparisons were made with a determination based on the total drug content in the aerosol units.

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 (Bricanyl, AB Draco, Sweden).

Each container was filled with a drug suspension corresponding to not less than 400 doses of 25 μl volume. For an assay on 10 separate aerosols by means of the NF XIV container sampling apparatus, 10 doses were released from each aerosol with one dose every 5 sec. The container was shaken between the actuations. The reception liquid consisted of 10 ml of chloroform and 20.00 ml of 0.005 mol/l sulphuric acid. The pressure tube was shaken for 1 min before the assay of the aqueous phase. The absorbance of the aqueous phase was measured at the maximum for terbutaline, 275 nm, and at 300 nm. The amount retained in the valve stem was determined by rinsing with ethanol–water 50 : 50 followed by spectrophotometric assaying after a reaction with 4-aminoantipyrine and potassium ferricyanide at pH 9.5 (Morén, 1978). The same aerosols were assayed by means of actuation under the surface of a reception liquid; 10 doses were released in 20 ml of chloroform with intermediate shaking of the aerosol container. After rinsing of the valve stem with chloroform, the sample liquid was transferred to a tube and shaken with 15.00 ml of 0.005 mol/l sulphuric acid, and the aqueous phase was assayed spectrophotometrically. After the sampling had been performed by means of actuation the total amount of terbutaline sulphate was determined in each aerosol unit. The contents were chilled in ethanol–solid carbon dioxide to about –50°C, and the container was opened cautiously. The propellants were allowed to evaporate slowly until a moist residue was obtained. The container and the separated valve components were shaken with 25 ml of chloroform and 25.00 ml of 0.005 mol/l sulphuric acid. The aqueous phase was assayed according to Morén (1978).

The density of the formulation, 1.4 g/ml, was used in the assays for the calculation of the concentration of terbutaline sulphate in mg/ml.

Statistical comparisons were made by means of paired *t*-tests as the assays were performed on the same aerosol units but after different sampling procedures.

RESULTS AND DISCUSSIONS

The results from determination of terbutaline sulphate after different sampling procedures are presented in Table 1. The procedure by means of the NF XIV container sampling apparatus without correction for valve stem retention resulted in a much lower value for the concentration compared with that based on the determination of the total content in the pressurized aerosol ($P < 0.001$). This is in accordance with the high valve stem retention found at the dose sampling from pressurized aerosols (Morén and Jacobsson, 1979). In the present study a 5 sec interval was used between the actuations, and it is probable that different results would be obtained if other intervals were used. By correction for valve stem retention, this source of error can be eliminated, but the results were still significantly lower than the concentration calculated from the total content ($P < 0.05$). The difference is probably due to an adherence of terbutaline sulphate to the container walls. In order to confirm this, a separate study was performed on 5 additional pressurized aerosols which were opened and emptied. After washing of the container with the propellant, trichlorofluoromethane, the residual amount of terbutaline sulphate was determined. The amount adhering to the walls of the container was found to be 2.6% (S.D. = 0.9) of the mean total content and this corresponds well with the difference between the methods.

The determination of the drug concentration by actuation under the surface of chloroform gave about 5% lower results than the container sampling apparatus ($P < 0.001$). The lower recovery appears to be due to a loss of drug substance with the bubbles passing the short distance through the chloroform layer. Because of the low recovery we do not consider the method to be satisfactory for determination of the drug concentration in the pressurized aerosol. It is possible that the recovery could be improved by a modified design of the reception container or by the use of a more efficient reception medium, but such modifications were not investigated.

In USP XX-NF XV the aerosol valve is primed by 10 actuations before sampling. When the priming is not followed by a washing of the valve stem before sampling, a certain amount of drug substance is added to the reception liquid. This amount will compensate for the low recovery in the procedure in an uncontrolled way.

TABLE 1

DETERMINATION OF TERBUTALINE SULPHATE AFTER DIFFERENT SAMPLING PROCEDURES

Sampling procedure	Terbutaline sulphate (mg/ml)	
Container sampling apparatus		
without correction	8.41 ± 0.28	a
with correction for valve stem retention	9.63 ± 0.15	a
Actuation in a reception liquid	9.11 ± 0.14	a
Assay of total content	9.83 ± 0.09	a

[a] $P < 0.001$. Mean values and S.D. from 10 aerosols.

An accurate determination of the total amount of drug substance in the pressurized aerosol can be made by the destructive method described above. A calculation of the concentration from the total amount can result in over-rated values, however, if the drug substance adheres to the container walls.

The procedure by means of the container sampling apparatus appears to be the best one tested for the purpose of determining the concentration, if a correction is made for valve stem retention as described in this paper. As the formulation of the pressurized aerosol in the present study is similar to that of other inhalation aerosols, we believe that the conclusions are also valid for other products.

ACKNOWLEDGEMENTS

We are grateful to Professor J. Sjögren and Mr. S. Hugosson for valuable discussions and Miss K. Persson for skilful technical assistance.

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