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Report

Turbuhaler: A New Powder Inhaler for Administration of Drugs to the Airways

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A metered-dose powder inhaler system has been developed. It is a multidose system that is easy to load and handle for the patient and that does not demand coordination between activation and inhalation. In addition, the new inhaler system is free of propellants, carriers, and other drug additives. Terbutaline sulfate has been selected as a suitable compound for evaluation of this inhaler. Clinical tests with the Turbuhaler have been performed and it has been compared with the conventional terbutaline pressurized metered-dose inhaler (MDI). The new powder inhaler can even be used at low inspiratory flow rates such as those present during acute asthma attacks.

KEY WORDS: terbutaline sulfate; bronchodilator; powder inhaler; Turbuhaler.

INTRODUCTION

Diseases in the airways can be treated systemically or by local administration of the drug to the target organ. Local administration of the drug has certain advantages over systemic treatment, as the treatment can be performed with smaller quantities of active compound and thus with fewer side effects. Systems currently available for local administration are nebulizers, metered-dose inhalers, and powder inhalers (1).

Administration of drugs by nebulization is an effective treatment but only for stationary use. Metered-dose inhalers (MDIs) are highly portable but side effects, most probably caused by the propellants and the lubricants, may occasionally occur (2). The main drawback with the MDIs, however, is problems in coordination between the release of the dose and inhalation (3). Powder inhalers currently available present no coordination problems but require a high inhalation flow for a good effect (4,5). Carriers such as lactose added to the active compounds often cause irritation at inhalation and the loading of a single dose is fairly complicated (4–7).

The development and use of spacer devices for metered-dose inhalers have shown the importance of inhalation systems where the requirement of coordination between dose release and inhalation is avoided (1,8).

The aim of this project was to develop an inhaler system free of propellants, carriers, and other drug additives: a multidose system that is easy to load and handle by the patient and that does not demand coordination between activation and inhalation (9–11).

TECHNICAL DESCRIPTION AND FUNCTION

The Turbuhaler was developed for small quantities of active compound, i.e., less than 1 mg per activation, without the use of any carrier compound and designed as a multidose unit. It is operated by the breathing air and is thus free from coordination problems. The inhaler can be loaded with drug substance to give at least 200 doses and each single dose is activated by a simple turning procedure. The inhaler is made from molded plastics and a spring in steel and the device consists of the following main parts (Fig. 1): (1) mouthpiece with insert, (2) bypass air inlet, (3) inhalation channel, (4) air inlet, (5) desiccant store, (6) window for dose indicator, (7) dose indicator, (8) storage unit for drug compound, (9) dosing unit, (10) operating unit, and (11) turning grip.

The dosing unit, 9, was constructed as a disk with groups of conical holes for the drug compound, 8, placed at the bottom of the storage unit (Fig. 2). The larger bottom areas of the truncated cones point toward the storage unit (Fig. 3). This orientation facilitates filling during the loading and emptying of the dosing unit at inhalation. The dosing system is thus based on a volumetric principle. Dosing is performed by rotating the dosing unit, 9, in the storage unit, 8, toward a pressure plate beneath the dosing unit, 9. Specially designed plastic scrapers placed just over the dosing unit will actively load the holes with the drug compound in a reproducible way. Thus forcible feeding of the active compound into the dosing unit makes the dosing of small compound quantities possible. The dosing is performed by simply twisting the turning grip, 11, back and forth.

When the patient inhales through the inhaler, the air enters a channel, 4, in the operating unit, 10, and passes a hole in the pressure plate and then the dosing unit, 9, for release of the dose loaded in the conical holes exposed to the area of the inhalation channel, 3. Drug aggregates are effectively deaggregated by the turbulent airflow in the inhalation channel, 3, and the insert of the mouthpiece 1. In order to produce an inhaler with a reasonable inhalation resistance, four bypass air inlets, 2, are placed below the mouthpiece, 1.

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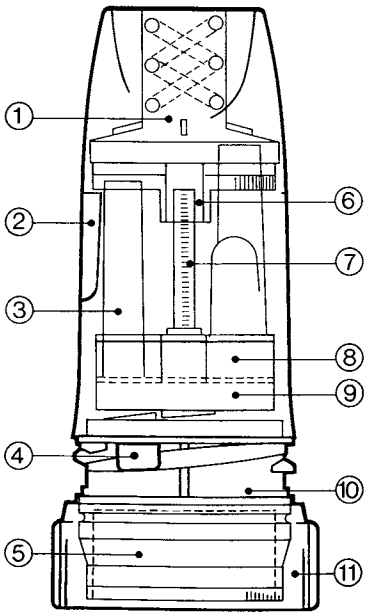

Fig. 1. The main parts of the Turbuhaler are the operating unit with a turning grip, the inhaler body with dosing unit, the storage unit for the drug compound and a dose indicator, and the mouthpiece with insert.

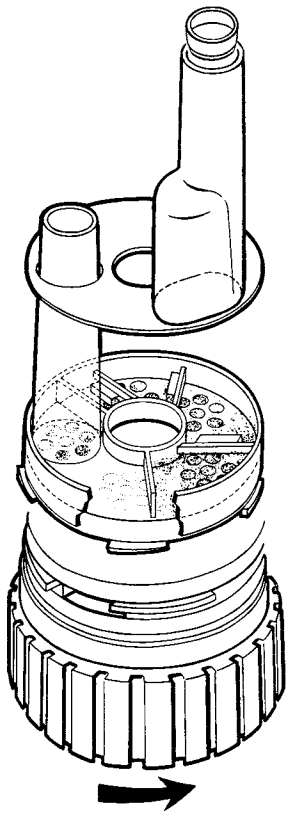

Fig. 2. Dispensing is performed by rotating the dosing unit in the storage unit toward a pressure plate beneath the dosing unit by a simple twisting back and forth of the turning grip.

The Turbuhaler has a dose indicator, 7, which will show a red sign in the window, 6, when there are 20 doses remaining in the inhaler.

Micronized terbutaline sulfate is transformed by spheronization into soft aggregates, which are hard enough to be handled and loaded into the inhaler but still easily broken up into primary particles during inhalation. This is essential, as the inhaler still must provide respirable particles for a good clinical effect at low inhalation flow rates, i.e., even at 20 liters/min. The formation of soft aggregates also minimizes disturbances for static charging. Terbutaline sulfate is not hygroscopic. However, the aggregates formed by spheronization will harden on the surface when exposed to moisture. This will influence the dosing characteristics and the ability of aggregates to break up into primary particles at inhalation. In order to protect the substance from moisture, the inhaler is provided with a desiccant stored in the operating unit of the inhaler. To achieve a tight closure, the cover and turning grip are screwed together. If the inhaler is stored (24 months) according to the instructions, sufficient drying capacity of the desiccant remains also for opening and dosing at least 200 times (the entire dose range) under extreme conditions (40°C/75% RH).

EVALUATION AND DISCUSSION

For terbutaline sulfate the dosing unit was constructed to give a nominal dose of 0.5 mg/dose. To study the metered-dose accuracy, the dose was released by a one-stage impactor at an airflow of 60 liters/min and a total aspiration volume of 2.0 liters. Terbutaline sulfate was then determined by a liquid chromatographic method. The metered-dose accuracy ($\bar{X} \pm$ SE) for four different batches was 0.51 ± 0.03, 0.51 ± 0.03, 0.51 ± 0.03, and 0.48 ± 0.05 mg. The mean dose for each batch is calculated from 10 single doses (doses 11–20) from each of 20 inhalers (12). This is a very satisfactory result. The nominal dose is, however, not a critical parameter for the clinical effect.

Ideally, particles should be approximately smaller than 5 μm in aerodynamic size for inhalation into the lungs (the respirable range) (13). The particle size distribution of terbutaline sulfate from the Turbuhaler was determined by a multistage liquid impactor at an airflow of 28.3 liters/min (Andersen Sampler). Respirable doses for four different batches were 189 ± 5, 205 ± 12, 201 ± 4, and 209 ± 18 μg/mg. Thus even at low flow rates 19, 21, 20, and 21% of the nominal dose is in the respirable range. The mean value for each batch is calculated from three consecutive determinations withdrawing five doses each time from the same Turbuhaler. Ten Turbuhalers have been analyzed (12).

Terbutaline sulfate administered via a pressurized dose inhaler is a well-established treatment for asthma and other diseases leading to bronchoconstriction. A cumulative dose–response study was therefore carried out to compare the Bricanyl Turbuhaler with the Bricanyl pressurized metered-dose inhaler. The forced expiratory volume in 1 sec (FEV_1) was used to estimate the bronchodilatory response. This study showed that equal bronchodilatation effects were obtained after treatment with the Turbuhaler and with a

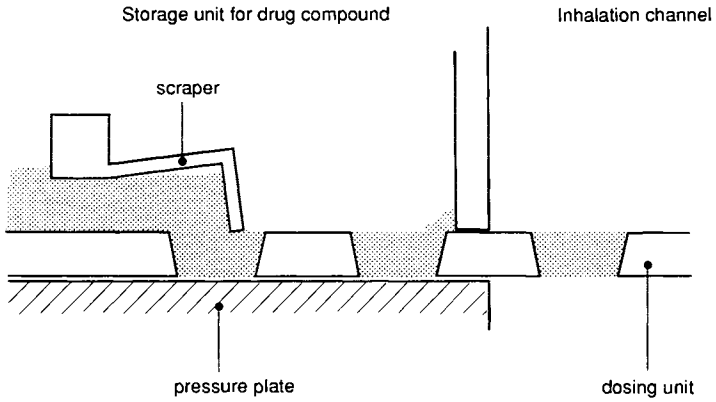

Fig. 3. The dosing unit is a disk with groups of conical holes placed at the bottom of the storage unit for the drug compound.

pressurized metered-dose inhaler (MDI) with terbutaline sulfate (14).

Studies in children have shown that the Turbuhaler with terbutaline is easy to use even during an acute asthma attack and that Turbuhaler treatment will have a good effect on children even at low inspiratory flow rates of about 20 liters/min such as those present during acute attacks (5).

The Turbuhaler has been compared to other inhalers presently available regarding ease of use and acceptability. Both children and parents expressed a preference for the Turbuhaler compared to the Rotahaler (4). The efficacy and acceptability of the Turbuhaler in adults were compared with those of the Bricanyl metered-dose inhaler. The Turbuhaler seems to be a valuable alternative to bronchodilator therapy with a metered-dose inhaler (15).

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