

DESIGN AND EVALUATION OF A NEW DRY POWDER INHALER

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ABSTRACT

Three versions of a new dry powder inhaler (DPI), RG-haler, were designed using two kinds of grid inserts. Salbutamol sulfate/lactose blend (Ventolin Rotacaps[®]) was selected as a model formulation to analyze the performance of all inhalers and compare their efficiency with three marketed devices (Rotahaler[®], Spinhaler[®] and ISF inhalator[®]) using the twin impinger (TI). Deposition of the drug in device was significantly ($p < 0.05$) lower for ISF inhalator[®] and all kinds of RG-halers in comparison with those of Rotahaler[®] and Spinhaler[®]. The amount of drug deposited in the stage 2 and the respirable dose for RG-halers were similar to those of ISF inhalator[®] and significantly ($p < 0.05$) higher than those of Rotahaler[®] and Spinhaler[®]. The results suggest efficient aerosol generating capability of the RG-haler.

Key words: Dry powder inhaler, Salbutamol sulfate, Twin Impinger, Respirable fraction

INTRODUCTION

Dry powder inhalers have become an increasingly popular alternative to the metered dose inhalers (1,2). These inhalers can be considered as ozone-friendly respiratory drug delivery systems, because they do not require chlorofluorocarbon (CFC) propellants to disperse the drug (3). The powder inhaler provides the advantage of coordinating inspiration by the patient's effort in creating a respirable cloud.

With some exceptions, micronized drug particles in most current commercial pharmaceutical dry powder inhalers are either aggregated or formed as an ordered mix with a coarse, inert carrier such as lactose. Depending upon the device, individual doses are contained either in gelatin capsules or foil blisters (4).

There are essentially two types in current commercial use. Those filled into a gelatin capsule that are basically single dose devices (e.g. Spinhaler[®], Fisons; Rotahaler[®], Glaxo). The others can be regarded as multiple dose devices (e.g. Turbuhaler[®], Astra; Diskhaler[®], Glaxo) (5).

A simple mean to empty a capsule is to pierce it by spins and pour out the powder. Rational design of the combination of the mouth-piece, air channeling and inlet through the device, and grids to deagglomerate the powder formulation results in a respirable dose that appears to be relatively appreciable.

This preliminary work was focused on the design and evaluation of the capabilities of all three versions of RG-halers in aerosolisation of a bronchodilator, salbutamol sulfate, in a marketed formulation (Ventolin Rotacaps[®]) in comparison with Rotahaler[®], Spinhaler[®] and ISF inhalator[®] devices.

MATERIALS AND METHODS

The solvents used in this study, all were of HPLC grade, and the water was glass-distilled. Salbutamol sulfate powder was obtained as a gift from Daroupakhsh Co. Bumethane sulfate was purchased from Sigma (UK). Methanol and phosphoric acid were obtained from Merck and ammonium dihydrogen phosphate from Aldrich. Rotahaler[®] and Ventolin Rotacap[®] are commercially available from Allen and Handburys, Division of GlaxoWellcome, Inc. Spinhaler[®], ISF inhalator[®] and materials used for fabrication of our inhalers were purchased from the market.

Inhaler design:

Computer Aided Design (AutoCAD, V.13) software was used to design the new inhalers with a great degree of accuracy. Three versions of inhaler were designed and fabricated (Figure 1). These versions were different in terms of the type

and number of the grids and were named as follows:

RG1-haler: with one grid by pores of the same diameters (1.5 mm).

RG2-haler: with two grids by pores of the same diameters (1.5 mm).

RG3-haler: with one grid by pores of different diameters (2.0, 1.5 and 1.0 mm).

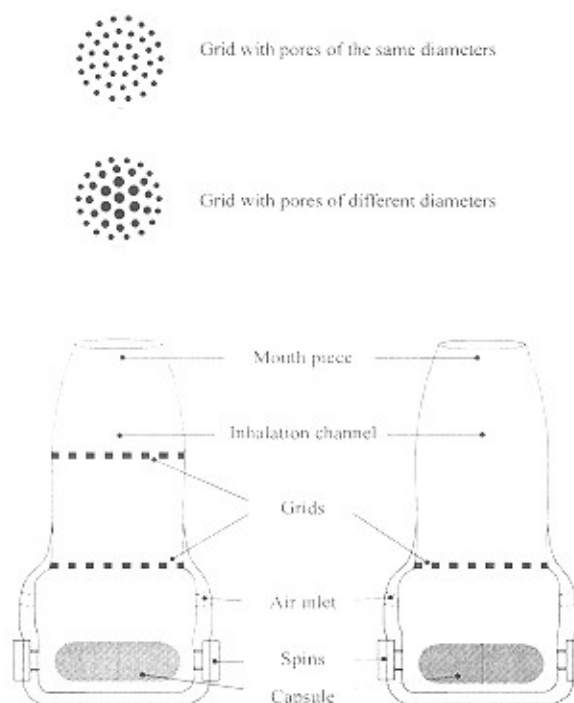


Fig 1. Schematic representation of the main parts of RG-halers.

Evaluation of the inhalers:

The initial Pharmacopoeial test of the inhalers was performed under the following condition:

The twin impinger experiment set-up (Figure 2) was as described in the British Pharmacopoeia (6). The mouthpiece of the DPI was fitted into the glass throat of the TI. Seven ml of purified water was placed in the upper stage and 30 ml in the lower stage of the TI as collection fluid. A flow rate of 60 (± 5) L/min through each device for 20 seconds was used. The device and TI glassware was then disassembled and rinsed with known volumes of purified water to collect drug deposited in the various areas.

Samples of salbutamol sulfate in solution were assayed by HPLC employing a mixture of water, methanol and phosphate buffer as a mobile phase running at a flow rate of 1.5 ml/min, bumethane sulfate as an internal standard and using UV

detection at 276 nm and a 30 cm x 4.6 mm i.d. micro-boundapack C_{18} column. Each concentration was corrected for dilution factors, and expressed as μg salbutamol sulfate recovered at each area. Percentage of the total amount recovered from each area was also calculated. Emitted dose was defined as the sum of that retained on the glass throat, upper and lower TI stages.

Each inhaler was tested on three occasions and means and standard deviations (SD) of the recovered drug in each area were calculated. Statistical analyses of differences between inhalers were performed and the results compared with Rotahaler[®], as the standard device marketed by Glaxo for inhalation of Ventolin Rotacaps[®], using student's unpaired *t*-test.

Better aerosol generating capability

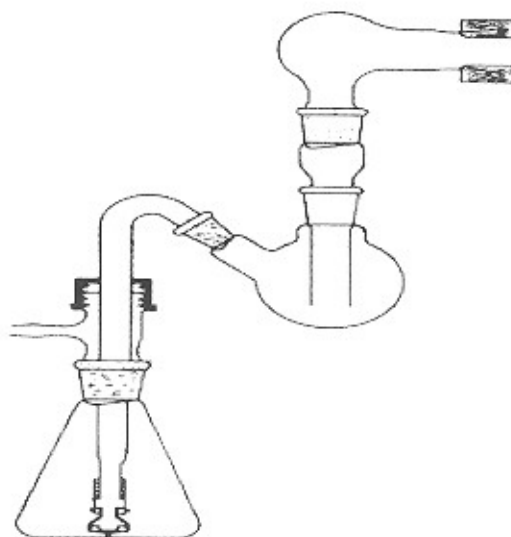


Fig 2. The Twin Impinger, the apparatus for the aerodynamic assessment of fine particles.

RESULTS AND DISCUSSION

Salbutamol sulfate standard curve was linear ($r=0.9997$) from 0.4 to 5.0 $\mu\text{g}/\text{ml}$ and it was unaffected by the presence of lactose.

Table 1 listed the mean \pm SD of the total amount of drug recovered from the device, capsule and TI for each inhaler. The mean of the data is expressed as a percentage of the labeled dose. Variations in the content of active ingredient remained in or emitted from the DPIs were found to be large in some cases, especially for Rotahaler[®]. The amounts of the drug remained in device for Rotahaler[®] (58.33 ± 7.65 μg) and Spinhaler[®] (41.08 ± 8.13 μg) were significantly ($p<0.05$) higher than those remained in the others. It was shown much more differences ($p<0.001$) with respect to the capabilities of some inhalers in emission of the drug from the capsules. Only the ISF inhalator[®] and all three types of RG-haler emitted a dose similar to their label claim. The emitted doses from both Rotahaler[®] and Spinhaler[®] were significantly ($p<0.05$) lower than those from the other devices.

Figure 3 shows the amount of the fine (dose fraction with aerodynamic diameter $< 6.4\mu\text{m}$) and coarse fractions emitted from the inhalators. The results showed the effect of the type of inhalers on fine particle fraction. Deposition of the drug

on stage 2 of the TI for ISF- inhalator[®] and all types of RG-haler were similar and all were significantly ($p<0.05$) higher than both Rotahaler[®] and Spinhaler[®]. It was found that the amount of drug deposited on stage 1 after using Rotahaler[®] and Spinhaler[®] was lower than the other devices. But by calculating the amount of drug in each stage as a percentage of the emitted dose for each device, deposition on stage 1 was significantly ($p<0.05$) lower for RG1-haler and RG2-haler. It means that after inhalation of salbutamol sulfate (Ventolin Rotacaps[®]) through Rotahaler[®] or Spinhaler[®], patients may receive lower amount of drug with higher coarse particles and lower respirable fractions.

These preliminary data provide encouraging indications of the aerosol generating capabilities of the RG-haler.

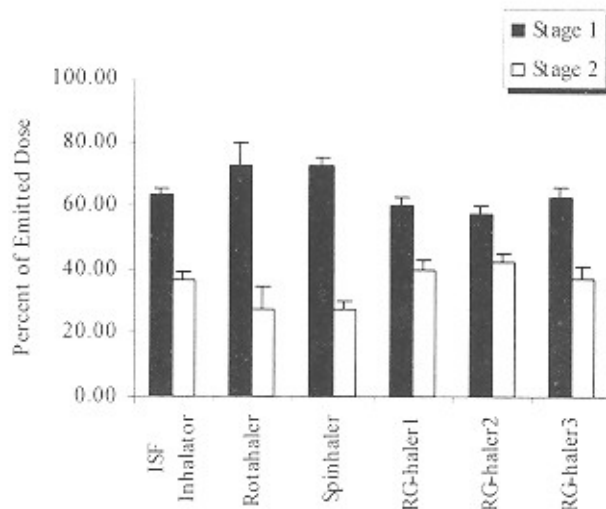


Fig 3. Comparison of the fine and coarse dose fractions as a percent of the emitted dose using various inhalers.

Table 1. The amount of salbutamol sulfate remained in device, capsule, and TI after aerosolization by various inhalers

Inhaler	Deposition in device		Deposition in capsule		Emitted dose	
	Mean (μg)	% LD [§]	Mean (μg)	% LD	Mean (μg)	% LD
ISF-inhalator	28.92 [*] (± 3.74)	14.46 [*] (± 1.87)	21.83 ^{**} (± 2.14)	10.92 ^{**} (± 1.07)	177.39 [*] (± 5.12)	88.70 [*] (± 2.56)
Rotahaler	58.33 (± 7.65)	29.17 (± 3.82)	82.00 (± 3.61)	41.00 (± 1.80)	106.04 (± 20.34)	53.02 (± 10.17)
Spinhaler	41.08 (± 8.13)	20.54 (± 4.06)	91.33 [*] (± 2.80)	45.67 [*] (± 1.40)	121.83 (± 11.41)	60.92 (± 5.70)
RG1-haler	32.33 [*] (± 1.15)	16.17 [*] (± 0.58)	19.70 ^{**} (± 2.46)	9.85 ^{**} (± 1.23)	194.75 [*] (± 3.25)	97.38 [*] (± 1.63)
RG2-haler	37.00 [*] (± 1.00)	18.50 [*] (± 0.5)	19.60 ^{**} (± 2.82)	9.80 ^{**} (± 1.41)	177.83 [*] (± 16.65)	88.92 [*] (± 8.33)
RG3-haler	36.33 [*] (± 3.51)	18.17 [*] (± 1.76)	17.57 ^{**} (± 2.63)	8.78 ^{**} (± 1.32)	185.36 [*] (± 14.24)	92.68 [*] (± 7.12)

[§]LD=Labeled Dose (200 μg). *P<0.05, **P<0.001, (n=3).

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