Performance of CFC free propellant- driven MDI of fluticasone propionate

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Metered dose inhalers (MDIs) of fluticasone propionate were developed for treatment of asthma and chronic obstructive pulmonary disease. MDIs with hydrofluoroalkanes based propellants were formulated with various doses, overages and various concentrations of alcohol. Optimum requirements were found as follows: effective valve delivery, overdoses (15%); 100% drug delivery, overages (20%); and emitted dose and fine particle fraction, alcohol content (5-10%).

Keywords: Emitted dose, Fluticasone propionate, Metered dose inhalers, Overages, Spray pattern, Valve delivery

Introduction

Metered dose inhalers (MDIs), vehicle for drug delivery into lungs, marketed prior to 1995 contained chlorofluorocarbons (CFC) as a propellant\textsuperscript{1,2}. Under Montreal Protocol\textsuperscript{3}, production and consumption of ozone layer depleting CFCs is banned in European Community and throughout developed world. Hydrofluoroalkanes (HFAs) as HFA 134a and HFA 227ea are two clinically proved alternative propellants in place of CFC propellants and dry powder inhalers\textsuperscript{4}. Fluticasone propionate (FP) is indicated for treatment of asthma and chronic obstructive pulmonary disease (COPD). These formulations greatly enhance therapeutic index of drugs, substantially diminishing number and degree of side effects without altering clinical utility. MDIs are more preferable than dry powder inhalers\textsuperscript{5,6}. This study presents preparation and evaluation of FP based MDIs by incorporating various concentrations of overdoses, overages and various proportions of alcohol.

Experimental Section

Materials

FP, HFA 134a (Zephex 134a), alcohol and oleic acid were of laboratory reagent grade, and Bespack valves and Bespack actuators were collected from NATCO. Dosage unit sampling apparatus for MDI (DUSA for MDI) includes Anderson cascade impactor (ACI), Twin stage impinger (TI), high performance liquid chromatography (HPLC), vacuum pump, flow meter, Pamasol filling crimping machine and capsules partial filling machine.

Formulation of HFA Based Metered Dose Inhalers (MDIs)

An accurately weighed FP (25 mg equivalent to 200 doses to deliver 125 mcg/ actuation) was suspended in alcohol (0.4 g, containing 4 mg oleic acid as surfactant), transferred into aluminium cans crimped with metered valve by Pamasol 2005 and filled with HFA 134a (10.3 g) by Pamasol 2005 propellant filling machine by pressure filling method. In similar manner, MDI formulations containing FP (50 mg equivalent to 200 doses to deliver 250 mcg/ actuation) was dissolved in alcohol (0.4g, containing 4 mg oleic acid as surfactant) and HFA 134a (10.3 g).

FP HFA MDI 125 mcg formulations were prepared with overdoses (0, 10, and 15%) to study effect of extra doses on valve delivery. Effect of overages on emitted dose was also studied from these formulations by incorporating overages (0, 5, 10, 15 and 20% w/w) to MDI formulation containing 15% overdose. To study effect of alcohol on spray pattern and leak rate, alcohol (0-20% w/w) was incorporated in MDI formulations and results were recorded (Table 1).

Evaluation of Metered Dose Inhaler (MDI) Formulations\textsuperscript{7-10}

Drug Compatibility

Compatibility of FP with alcohol, oleic acid and HFA was investigated with HPLC technique. FP (20 mg) was put into a volumetric flask (100 ml). Drug was dissolved

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Table 1—Characterization of MDI formulated with various concentrations of alcohol

<table>
<thead>
<tr>
<th>Formulation (% alcohol)</th>
<th>Leak rate, % per year (n=3)</th>
<th>Valve delivery, mg (n=10)</th>
<th>Net fill weight, g (n=5)</th>
<th>Spray pattern, mm (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.1 ± 0.1</td>
<td>63 ± 4</td>
<td>17.0 ± 0.2</td>
<td>12.1 ± 0.2</td>
</tr>
<tr>
<td>2.5</td>
<td>1.9 ± 0.2</td>
<td>64 ± 3</td>
<td>17.6 ± 0.6</td>
<td>15.5 ± 0.1</td>
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<tr>
<td>5.0</td>
<td>1.9 ± 0.3</td>
<td>64 ± 3</td>
<td>10.4 ± 0.4</td>
<td>12.9 ± 0.3</td>
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<tr>
<td>7.5</td>
<td>2.1 ± 0.1</td>
<td>64 ± 5</td>
<td>10.5 ± 0.2</td>
<td>13.5 ± 0.2</td>
</tr>
<tr>
<td>10.0</td>
<td>2.5 ± 0.2</td>
<td>62 ± 3</td>
<td>10.8 ± 0.3</td>
<td>13.9 ± 0.2</td>
</tr>
<tr>
<td>15.0</td>
<td>2.9 ± 0.3</td>
<td>64 ± 4</td>
<td>10.6 ± 0.4</td>
<td>14.9 ± 0.3</td>
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<tr>
<td>20.0</td>
<td>2.5 ± 0.1</td>
<td>69 ± 3</td>
<td>10.5 ± 0.3</td>
<td>15.9 ± 0.1</td>
</tr>
</tbody>
</table>

N, number of replications

Fig. 1 - Compatibility chromatograms of Fluticasone propionate (FP) MDI: a) FP placebo chromatogram; b) FP standard chromatogram; and c) FP sample chromatogram
in a mixture of buffer (pH 2.5) and methanol (45:55) (mobile phase). It was sonicated and diluted with mobile phase up to the mark. Resulting solution was suitably diluted and injected into column. Nova-pak C<sub>18</sub> (3.9 mm x 150 mm, 4µ) column was used and maintained at 30°C. Flow rate of mobile phase was maintained at 2.5 ml/min for 18 min runtime. Sample was detected at 220 nm. HPLC used with samples alcohol, HFA, FP and formulation containing FP, alcohol, oleic acid and HFA. Contents from pressurized container were discharged by actuating valve at 5s intervals and recorded number of doses discharged.

**Leak Test**

Aerosol containers (12) were selected randomly, and date and time recorded to the nearest of ½ h. Each container weighed to nearest mg, and recorded weight as W<sub>1</sub>. Containers allowed to stand in an upright position at room temperature (RT) for 3 days and again weight of each container recorded as W<sub>2</sub> and recorded date and time to nearest ½ h (T). Leakage rate (mg/y) from each container was calculated as

\[
\text{Loss (mg/y)} = \frac{365 \times 24 \times (W_1 - W_2)}{T}
\]

\[
\text{Leakage ( %)} = \frac{\text{Loss} \times 100}{\text{Net fill weight}}
\]

**Spray Pattern**

Contents of pressurized container were sprayed on glass slide to check spray pattern shape and dimensions.

**Valve Delivery**

Aerosol container weighed with a clean actuator. Removed actuator and replaced with another actuator and dispensed one dose. Again replaced with original clean actuator and re-weighed. Recorded weight of each individual dose dispensed. Calculated average weight of 10 doses delivered through valve and reported as valve delivery.

**Stability Studies**

FP HFA MDI 125 mcg were tested after 6 months stored in aluminum cans at 40°C/75% RH and 25°C/60% RH and evaluated for assay, number of doses delivered, deposition of emitted dose and net fill weight. Samples were collected at regular intervals and analyzed.

**Results and Discussion**

Compatibility studies with excipient indicated identical chromatograms (Fig. 1) and found to be compatible. MDIs, developed with FP, were incorporated with extra doses (0, 10 and 15%) to study effect of extra doses on valve delivery. Observed valve delivery rates (Fig. 2) indicated that 130 doses are required to deliver 200 doses, each containing 125 mcg/dose and suggested to use 15% extra doses for effective valve delivery.

Effect of overages on emitted dose was studied from these formulations by incorporating overages (0, 5, 10,
15 and 20% w/w) to MDI formulation containing 15% overdose. Observed emitted doses in presence of overages (Fig. 3) indicated the need of 20% overages for 100% drug delivery, and to prevent inevitable retained losses either from inhaler device or from valve. An additional 35% formulation (> labeled claim) is required to deliver completely specified doses from MDI device.

FP MDI formulations were evaluated for emitted dose and fine particle fraction with twin impinger apparatus and samples were tested with HPLC. Emitted dose and fine particle fractions were found inversely proportional to alcohol content (Fig. 4). High fine particle increase and low emitted dose was observed at 20% alcohol content, may be due to solubilization of drug in alcohol and hence suspension formulation recommended for FP. Alcohol content (5-10% w/w) is preferred to get optimum emitted dose and fine particle fraction.

To determine influence of actuator orifice diameter on emitted dose and fine particle deposition, three different actuator diameters (0.22, 0.33 and 0.48 mm) were employed. Same parameters were also tested with twin impinger and all samples were analyzed with HPLC. In case of FP HFA MDI formulations (125 and 250 mcg), emitted dose was very low (< 80%) with 0.22 mm
actuator. Fine particle fraction with 0.33 mm actuator was good in both formulations compared with other two actuators. Based on results (Fig. 5) for FP formulations, 0.33 mm actuator is finalized.

Stability studies, carried out for HF A MDI formulations of Fluticasone 125 mcg, at 40°C/75% RH and 25°C/60% RH, showed that these products are stable at these conditions (Table 2).

**Conclusions**

HFA based MDIs were developed for FP. In pressurized MDI formulation, overages were required to prevent inevitable retentive losses and to deliver 100% drug to patient. An extra 20% of overages and 5-10% w/w alcohol content are recommended to get optimum emitted dose and fine particle fraction. Actuator with 0.33 mm was selected. All developed MDIs met pharmacopoeial requirements. Recommended storage condition for metered dose is 25°C/65% RH.

**Acknowledgements**

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**References:**


Table 2—Stability data of Fluticasone HFA inhaler 125 mcg stored at 40±2°C / 75±5%RH & 25±2°C / 60±5%RH

<table>
<thead>
<tr>
<th>Characteristics tested</th>
<th>Results at testing intervals</th>
<th>Initial</th>
<th>1 month</th>
<th>2 month</th>
<th>3 month</th>
<th>6 month</th>
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<td>Assay (%)</td>
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<td>101.4</td>
<td>101.2</td>
<td>95.7</td>
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<tr>
<td>No. of doses</td>
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<td>132</td>
<td>129</td>
<td>128</td>
<td>127</td>
<td>125</td>
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<tr>
<td>Deposition of emitted dose, %</td>
<td></td>
<td>27.5</td>
<td>26.9</td>
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<td>Net fill weight, g</td>
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<td>11.2</td>
<td>11.1</td>
<td>10.9</td>
<td>10.9</td>
<td>10.8</td>
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</table>

<table>
<thead>
<tr>
<th>Characteristics tested</th>
<th>Results at testing intervals</th>
<th>Initial</th>
<th>3 month</th>
<th>6 month</th>
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<tr>
<td>Assay (%)</td>
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<td>97.3</td>
<td>98.7</td>
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<td>Deposition of emitted dose, %</td>
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<td>27.6</td>
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<tr>
<td>Net fill weight, g</td>
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<td>11.2</td>
<td>11.0</td>
<td>10.8</td>
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