The formulation and evaluation of a CFC-free budesonide pressurised metered dose inhaler

D. Ganderton*, D. Lewis, R. Davies, B. Meakin, T. Church

Vectura Limited, 1 Prospect West, Chippenham, SN14 6F4, UK

Summary  Although dry powder inhalers are well established for the delivery of corticosteroids, the pressurised metered dose inhaler remains the preferred and most cost effective presentation. To design an HFA solution formulation which matched marketed CFC products (Pulmicort® and Desonac® DA) two elements of the Chiesi Modulite® system, the addition of a non-volatile component and the actuator orifice diameter, were varied. These variables, which were shown by in vitro tests to influence the fine particle dose and its mean particle size in different ways, could be permuted to give an aerosol cloud with size characteristics very close to the comparator products. The likelihood that this would confer clinical equivalence is reinforced by a pharmacokinetic analysis which showed that the chosen HFA solution formula gave similar systemic absorption from the lung as Pulmicort®. The equivalence in aerosol characteristics was sustained when the pressurised metered dose inhalers (pMDIs) were used with spacers. The Chiesi Jet® and the AstraZeneca Nebuhaler®, when used with their respective pMDIs, reduced likely oropharyngeal deposition to the same extent and gave a similar increase in the fine particle dose.

Introduction

Budesonide, delivered directly to the lung, has played a major role in establishing corticosteroids as a mainstay of asthma treatment. Although introduced as a pressurised metered dose inhaler (pMDI), its clinical success was greatly influenced by reformulation as a more efficient multidose dry powder inhaler (DPI), Turbuhaler®. Thorsson et al.¹ showed that in this form, the lung deposition was approximately twice that of the pMDI. Other dry powder inhalers are now under development, capitalising on the perceived disadvantages of Turbuhaler® and addressing issues such as the generation of adequate flow rates, the effect of inspiration manoeuvre on the dose received by the patient, cost and patient preference. Using lung deposition and pharmacokinetics measures, Ball et al.² showed that the low-cost Miat Monohaler® could be used in groups of patients, such as children, unable to inhale maximally through Turbuhaler®. Hirst et al.³ compared lung deposition from two DPIs, Easyhaler® and Turbuhaler®, using a pMDI plus spacer (Nebuhaler®) as a reference standard. Patients preferred the Easyhaler® although the two DPIs were of comparable efficiency. Similar conclusions were drawn by Frew et al.⁴ when the novel DPI Airmax® was compared to Turbuhaler®.

Despite these developments, there remains great clinical demand for a pMDI delivering budesonide. pMDIs are small, portable devices used by almost 80% of asthmatic patients. In an extensive review comparing the effectiveness of inhaler devices, the findings of Brocklebank et al.⁵ were that measures of pulmonary function, symptom scores and adverse event gave no difference in clinical efficacy.
between a pMDI with or without spacer and a DPI for the delivery of corticosteroids. At present, therefore, a budesonide pMDI will be the most cost effective presentation. However, in developing such a product two issues should be addressed; the replacement of the chlorofluorocarbon (CFC) propellants currently used and the perceived problems patients may experience in coordinating dose generation and inspiration.

Propellant replacement in pressurised metered dose inhalers

The general environmental issues related to the used of CFCs and their replacement hydrofluoroalkanes (HFAs) are well known. However, their replacement in pMDIs has presented the pharmaceutical industry with acute problems which relate to the solubility of drugs and excipients. If the drug is insoluble in the HFA, it can be reformulated as a suspension, like the CFC product, with the aim to yield an aerosol with a similar particle size distribution of the cloud and a similar pattern of deposition in the lungs, ultimately eliciting the same clinical response. At a given dose, the two formulations will be bioequivalent and transition to the new formulations will be straightforward. The problem now to be solved is the stabilisation of the suspension in circumstances in which the usual excipients, such as sorbitan trioleate, are inadequately soluble in the replacement HFA. Tansey describes the addition of ethanol to dissolve oleic acid, the stabiliser used for salbutamol sulphate in Airomir. Cripps et al. describe the transition to stable non-CFC suspension formulations of salbutamol and fluticasone propionate which contain no excipients other than the propellant. However, budesonide, like beclometasone dipropionate (BDP), has a significant solubility in the replacement propellants. A stable suspension product cannot be devised and the drug must be formulated as a solution. In a pMDI containing a simple solution, the size of the particles produced will be determined by the size of the droplets emerging from the actuator and the concentration of drug they contain, factors which combine to form an ultra-fine cloud. When Leach devised the Qvar solution formulation of BDP, the average particle size was reduced from 3 to 4 μm observed with the CFC suspension formulation to only 1.1 μm. More pervasive delivery to lung allowed the effective dose to be halved. The advantages and disadvantages of this development have been assessed by Tashkin. Clearly, there is potential for a higher ratio of therapeutic efficiency to side effects although the larger amount delivered to the lung periphery may increase systemic absorption despite the lower dose. However, major disadvantage of such formulations is the revision of existing dosage regimens. A better procedure is to modify the characteristics of cloud generated by the HFA formulation to match that of CFC product it is to replace, thus preserving dosage schedules. The Chiesi Modulite system, described by Ganderton et al., may be used to achieve this seamless transition.

The formulation of a budesonide pMDI using Modulite

Modulite changes the speed and particle size of aerosol clouds by permuting four variables: the non-volatile components of a solution formula, the actuator orifice geometry, the volume of the metered solution and the vapour pressure of the propellant. To achieve a satisfactory match with suspension formulations, exemplified by Pulmicort® and Desonac DA®, only two variants, the non-volatile component and the actuator orifice, were employed.

An added non-volatile component would increase the size of aerosol particle once the propellant had evaporated to values close to those observed in suspension formulae. Ethanol would be added to ensure adequate solubility of budesonide. The observed solubility arising from the interaction of these constituents, together with water, the ingress of which arises from the hygroscopic nature of the chosen propellant HFA134a, is described by the phase diagram in Fig. 1 which defines the region in which a homogenous solution is obtained.

The effect of decreasing the aperture of the actuator orifice is to reduce efflux of the solution through the metering valve. The speed of the cloud is reduced without significant change in its particle size distribution. This reduces oropharyngeal capture and leads to the delivery of more particles to the lung.

The demonstration that permutation of these factors gives a product equivalent to, say, Pulmicort® ultimately requires clinical investigation. However, meaningful in vitro tests can be carried out to assess a large number of variants which arise in a Modulite® programme. A selected variant can then be subjected to a pharmacokinetic evaluation to reinforce selection for clinical evaluation.
The in vitro evaluation of Modulite® budesonide pMDIs

The aerodynamic diameter of a particle is the primary determinant of capture in the respiratory tract. It accommodates the density of the material and determines the inertial behaviour during flight, leading to arrest by impaction and sedimentation. In vitro models simulating these effects are well established in product development and are accepted by regulatory authorities. The generated aerosol is led via a carefully specified inlet or throat into a multi-stage inertial impactor which divides the cloud into a number of fractions depending on aerodynamic diameter. The distribution of drug mass in these fractions may be tabulated or expressed as a median with a specified distribution, mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD), respectively. A fine particle dose may also be derived. This is the mass of drug in particles less than 5 μm, considered likely to reach the lung. Material depositing in the throat is more likely to be captured in the oropharynx.

In Fig. 2, these principles are applied to formulations metering 200 μg budesonide and containing different concentrations of glycerol which modulated the MMAD around the target without having a significant effect on the fine particle dose. Opposite effects occur when the actuator orifice is varied. Fig. 3 shows that when the orifice diameter is decreased from 0.42 to 0.22 mm, the MMAD is only slightly decreased whereas there is a large increase in fine particle dose from 30.5 to 85 μg.

These experiments led to the selection of a formula containing 15% ethanol and 1.3% glycerol in HFA134a, metering 50 μl of solution containing 200 μg budesonide equipped with an actuator with an orifice 0.42 mm in diameter. A detailed in vitro deposition pattern of this formula is compared with Pulmicort® and Desonac DA® in Fig. 4. Simplified
data comparing the fine particle dose of the three products is given in Fig. 5. The data shows that the Modulite® experimental programme has produced an HFA solution formulation which is a close match to the established suspension formulations propelled by CFCs.

**Comparative pharmacokinetic evaluation of budesonide formulations**

The development of very sensitive analytical methods permits quantification of small blood levels following pulmonary administration. Such systemic exposure is a useful comparative measure. For example, Acerbi et al.11 compared the blood level profile of budesonide epimers following the administration of 1600 μg budesonide to volunteers using a solution pMDI equipped with actuators with 0.3 or 0.42 mm orifice apertures. The experiments were conducted with mouth rinsing to ensure that systemic absorption arose primarily from the lung. The pharmacokinetic data is show in Table 1.

![Figure 5](image) Fine particle dose of budesonide HFA 200 μg, Desonac® DA and Pulmicort® 200 μg.

Significantly higher AUC values were obtained with the finer aperture reflecting the higher fine particle dose and lower MMAD observed in the in vitro evaluation (Fig. 3). The same experimental procedure was used to compare the selected HFA solution formulation with Pulmicort® CFC pMDI and Pulmicort Turbuhaler®. Plasma concentrations, given in Fig. 6, show that when the 0.42 diameter actuator is used with the HFA formula, a pharmacokinetic profile similar to the reference products is obtained.

**The effect of spacers on the delivery of budesonide**

In presenting corticosteroids as pMDIs, the major disadvantages are coordination of dose generation with inspiration and the extensive deposition which occurs in the buccal cavity. The latter may cause local side effects or, after swallowing, significant systemic availability. Both disadvantages may be overcome in large part by the use of holding chambers or spacers. They are of particular value with children and with adults when large doses of corticosteroids are prescribed. Thorsson and Edsbacker13 evaluated a Pulmicort® pMDI with and without a Nebuhaler®, a large volume spacer, and showed that the spacer retained about half the dose and that the dose delivered to the lung (32.6%) was almost double that of the pMDI alone (18.3%). This is a very favourable change in the balance between wanted and unwanted deposition, oropharyngeal capture being <10% when the spacer was used. An interesting error in the study occurred when canisters attached to the spacer were not shaken between puffs so that contents were not evenly suspended. This resulted in a decrease in lung delivery, the systemic availability via the lung being reduced by a half. Such

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BUD HFA 0.30</th>
<th>BUD HFA 0.42</th>
<th>HFA 0.30/HFA 0.42 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 R epimer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>1.77 (0.46–2.78)</td>
<td>1.66 (0.5–1.97)</td>
<td>1.07</td>
</tr>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>0.17 (0.17–0.33)</td>
<td>0.17 (0.17–0.33)</td>
<td>—</td>
</tr>
<tr>
<td>AUC (ng h/ml)</td>
<td>4.10 (1.44–5.58)</td>
<td>2.20 (1.90–3.43)</td>
<td>1.86</td>
</tr>
<tr>
<td>( t_{1/2\text{el}} ) (h)</td>
<td>2.21 (1.93–3.07)</td>
<td>2.20 (1.84–2.77)</td>
<td>1.00</td>
</tr>
<tr>
<td>22 S epimer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>1.82 (0.49–3.13)</td>
<td>1.78 (0.58–2.38)</td>
<td>1.02</td>
</tr>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>0.17 (0.17–0.33)</td>
<td>0.17 (0.17–0.33)</td>
<td>—</td>
</tr>
<tr>
<td>AUC (ng h/ml)</td>
<td>4.83 (1.52–7.12)</td>
<td>3.27 (2.14–4.82)</td>
<td>1.48</td>
</tr>
<tr>
<td>( t_{1/2\text{el}} ) (h)</td>
<td>2.35 (1.37–4.32)</td>
<td>2.90 (1.95–3.50)</td>
<td>0.81</td>
</tr>
</tbody>
</table>
effects are not possible with a Chiesi Modulite® solution formula because no phase separation can occur.

In Chiesi’s Jet®, the spacer, the actuator and the canister containing the budesonide HFA formula are integrated to give a compact unit. Using the in vitro model described above, its effect on the delivered dose and its particle size distribution is compared with the pMDI alone in Fig. 7. Massive oropharyngeal capture from the pMDI, simulated by throat deposition, is largely transferred to the Jet® and the amount of drug delivered to the lower stages of the impactor, which simulates lung delivery, is increased. The cumulative value of drug ≤5 μm is 50.5 μg with Jet® compared to 31.3 μg without. The comparison with Pulmicort® pMDI plus Nebuhaler® is made in Fig. 8. This gives a fine particle dose of 50.5 μg for budesonide Jet® and 52.5 μg Pulmicort® pMDI, showing how closely the novel HFA formulation
matches the Pulmicort® when presented in a spacer configuration.

Conclusions

Despite the intrinsic fineness of HFA solution pMDIs and its effect on pulmonary deposition, a strong case can be made for matching such products to their coarser CFC suspension counterparts to allow substitution without change of dose. This can be achieved using the Chiesi Modulite® technology. By varying the concentration of a non-volatile component in the solution and the actuator orifice diameter, a product was designed which gave an aerosol which, when assessed in an in vitro model, was similar in fine particle content and size distribution to CFC comparator products, suggesting that these products would be clinically equivalent. This is reinforced by a pharmacokinetic analysis following administration of these products to volunteers which showed similar systemic absorption from the lung. This equivalence in aerosol characteristics was sustained when the pMDIs were used with spacers. The Chiesi Jet® and the AstraZeneca Nebuhaler® reduced likely oropharyngeal deposition to the same extent and gave a similar increase in the fine particle dose.

References

1. Thorsson L, Edsbacker S, Conradson T-B. Lung deposition of budesonide from Turbuhaler® is twice that from a pressurised metered dose inhaler P-MDI. Eur Resp J 1994; 7:1839-44.