Modulite®: a means of designing the aerosols generated by pressurized metered dose inhalers

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Abstract

Although popular, the pressurized metered dose inhaler generates coarse, fast moving clouds so that the fraction reaching the lung is small. These shortcomings can be redressed by Modulite® which permutes the following 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 propellants. This permits the design of aerosols with chosen particle size and plume speed. This facilitates co-ordination of dose generation with inspiration, reduces oropharyngeal deposition and provides a mechanism for targeting drug delivery to different parts of the lung. These principles are exemplified by designing an HFA-propelled beclometasone dipropionate product which closely matches existing products which use chlorofluorocarbons.

INTRODUCTION

For almost 50 years the use of pressurized metered dose inhalers (pMDIs) has been enormously successful in the treatment of asthma and obstructive airways disease. However, success has been derived far more from forgiving therapeutic indices of drugs such as salbutamol and patient preferences than from the intrinsic properties of the dosage form. As a delivery vehicle it is far less precise than other dosage forms. The dose is generated at a high speed, typically 30 m sec⁻¹, over a very short period, typically 200 msec. This creates serious problems for patients in co-ordinating dose generation with an appropriate inspiration and most of the drug impacts in the throat and is swallowed. Although these problems can be eased by the use of spacers, the dose given becomes even more variable depending on the pattern of use.

The banning of the environmentally damaging chlorofluorocarbons (CFCs) is denying the pharmaceutical industry the propellants used hitherto. This has created serious problems because the newly approved hydrofluoroalkane propellants, HFA 134a and HFA 227, have very different properties that their predecessors which complicate product replacement. However, the situation does offer an opportunity to re-examine the pMDI, retaining its strengths and eliminating its weakness. The Modulite® technology achieves this objective.

THE EFFICIENT DELIVERY OF DRUGS TO THE LUNG

To deliver drugs optimally to the lung requires close integration of the device used, the formulation it contains and the inspiratory manoeuvre made by the patient. The objective is the formation of a slow moving cloud containing particles of the required particle size. It should be generated over a relatively long period of time which permits co-ordination with a slow inspiration by the patient. Modulite® achieves these objectives primarily by permuting the two interdependent variables: the addition of a non-volatile component to the formulation and the geometry of the actuator orifice. Two minor variables, change in vapour pressure by mixing available propellants and the volume of the metering valve, are also used to refine performance.

THE USE OF NON-VOLATILE COMPONENTS

The primary determinant of capture in the lung is the aerodynamic size of a particle. This characterizes the particle’s inertial behaviour – i.e. its ability to cross streamlines when entrained in an airstream and its rate of sedimentation in a gravitational field. It is largely defined by the density and diameter of the particle. Although the former is exploited in some specialized formulae using porous particles, the size of simpler solid particles is the main variable used by the formulator.

Since particles vary about some average value, it is usually expressed as a mass median aerodynamic diameter (MMAD) and values of 1 to 5 μm are generally accepted as suitable for pulmonary delivery. Particles at the high end of this range would deposit centrally in the larger conducting airways whereas very fine particles would reach the lung periphery. In many formulations,
the fraction of the cloud in this size range is quite small and is commonly expressed as the fine particle dose (FPD) i.e. the fraction of the label claim < 5 μm.

Existing CFC products invariably contain solid particles milled to a fine size and include them as a suspension in the propellant. Milling is a poorly controlled process dominated by the physical properties of the drug crystals, such as hardness and lattice flaws. Since the resultant size dominates the characteristics of the cloud produced by the formulation, the latter cannot be optimized.

An alternative, used in the Modulite® technology, is to dissolve the drug in the propellant with the aid of a co-solvent such as ethanol. This brings important advantages in performance consistency. Phase separation occurs naturally in suspension formulas and variation in shaking and storage in the hands of patient can affect dose uniformity and the size distribution of the dose. The spray content and pattern from solution formulations is much more consistent. More importantly, since the spray pattern is determined largely by the vapour pressure of the propellant, the proportion of co-solvent and the dimensions of the actuator orifice, it can be controlled.

The final particle size distribution then depends on the drug concentration in a droplet and any other non-volatile components which have been added. The permutation of these factors allows the design of a product with a chosen particle size distribution.

With a simple solution, each droplet will dry to give a particle, the size of which depends on the concentration of the drug in the solution. In practice, the MMAD of such formulations is very small with typical values of 0.8–1.2 μm. This is the lower end of the useful range, yielding a product targeted largely to the alveoli. To deliver drug to other chosen regions, a systematic means of making somewhat coarser particles is necessary. With Modulite® a non-volatile component, chosen to give no pulmonary hazard, is included at the level which gives the required enhancement of size. Such changes in cloud size may be explained simply in terms of the volumetric contribution of the non-volatile component. Assuming that the cloud particles approximate to a spherical geometry, the size, d, is related to volume, V, by the equation:

\[ d = \left(\frac{6V}{\pi}\right)^{\frac{1}{3}} \]  

Assuming that atomization patterns are unchanged, this size may be increased from a baseline value of \(d_0\) to \(d_1\) by increasing the volume of the non-volatile components from \(V_0\) to \(V_1\), so that:

\[ d_1 = d_0\left(V_1/V_0\right)^{\frac{1}{3}} \]  

For a given combination of drug, non-volatile excipient and propellant and assuming that the spray pattern is maintained and density changes are small as the composition varies, the diameters in equation 2 can be replaced by MMAD to give:

\[ \text{MMAD}_1 = \text{MMAD}_0 \left(\frac{m_1}{m_0}\right)^{\frac{1}{3}} \]  

where \(m_0\) is the mass of drug in the simple formula of drug, co-solvent and propellant and \(m_1\) is the mass of drug plus non-volatile additive.

The experimental data from Table 1 are plotted in Figure 1. It shows that simple formulas containing a dose of beclometasone dipropionate (BDP) of 50 μg or 250 μg have an MMAD of 1.1 and 1.8 μm, respectively.

The MMAD can be increased with non-volatile additives and, for example, the inclusion of 6% of a polyethylene glycol gave an average value of 4.25 μm. These experimental data are plotted in Figure 2 against the theoretical dimensions derived from equation 3 and close agreement is observed.

THE EFFECT OF ACTUATOR ORIFICE

The effect of actuator geometry on cloud formation has been known since the early work of Polli et al. (1) who showed that a larger orifice produced a coarser spray. However, exploitation of this phenomenon has been limited by the use of suspensions which clog finer apertures below, say, 0.3 mm. The solution technology used in Modulite® frees the formulation from this constraint so that variation in aperture diameter and length can be permuted with other variables in designing products to a given specification. More importantly, the use of fine orifices generates slow moving clouds over a much longer period. This reduces oro-pharyngeal deposition and greatly facilitates the co-ordination of cloud generation with the inspiration of the patient, overcoming a serious problem commonly encountered with existing pMDIs.

Figure 3 describes the changes in the cloud characteristics generated from a formula containing 0.424% w/w BDP, 1.3% w/w glycerol and 15% w/w ethanol in HFA when the actuator orifice diameter is varied from 0.14 to 0.42 mm. This has profound changes on the fraction of the spray which evaporates to form respirable particles. In the in vitro model used for assessment, the output from an inhaler is led through a right-angled throat to simulate losses in the oro-pharynx before entry into an impactor which measures aerodynamic particle size. Use of fine orifices massively reduces these losses so that a larger fraction of the delivered dose is presented as a fine particle dose less than 5 μm. MMAD of this fraction becomes only slightly finer, decreasing from 2.9 μm to 2.5 μm over the range studied. This is explained by the data given in Table 2 which shows the MMAD generated by the different actuators and the variation in size around this mean expressed as a geometric standard.
Table 1. Effect of non-volatile components on BDP-HFA 134a solution pMDI characteristics: mean ± SD (n ≥ 3)

<table>
<thead>
<tr>
<th>Formulation (% w/w)</th>
<th>BDP</th>
<th>Ethanol</th>
<th>Glycerol</th>
<th>PEG 400</th>
<th>HFA 134a</th>
<th>Delivered dose (µg)</th>
<th>Fine particle dose (µg)</th>
<th>MMAD (µm)</th>
<th>GSD</th>
<th>Replicates</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.085a</td>
<td>14:0</td>
<td>14-0</td>
<td>1.0</td>
<td>85-9</td>
<td>83-9</td>
<td>43.2 ± 1.9</td>
<td>14.7 ± 0.7</td>
<td>1.1 ± 0.1</td>
<td>2.2 ± 0.1</td>
<td>6</td>
</tr>
<tr>
<td>0.424b</td>
<td>15:0</td>
<td>15-0</td>
<td>1-0</td>
<td>84-6</td>
<td>83-6</td>
<td>222.1 ± 5.1</td>
<td>65-9 ± 4.2</td>
<td>1.8 ± 0.2</td>
<td>2.2 ± 0.1</td>
<td>6</td>
</tr>
<tr>
<td>0.424b</td>
<td>15:0</td>
<td>15-0</td>
<td>1-6</td>
<td>83-6</td>
<td>83-0</td>
<td>227.9 ± 3.6</td>
<td>51-8 ± 1.6</td>
<td>2.9 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>2</td>
</tr>
<tr>
<td>0.424b</td>
<td>15:0</td>
<td>15-0</td>
<td>6-1</td>
<td>83-0</td>
<td>78-5</td>
<td>230.7 ± 232.6</td>
<td>45-7 ± 46-7</td>
<td>3.1 ± 1.3</td>
<td>3-2-3</td>
<td>2</td>
</tr>
</tbody>
</table>

Actuator orifice 0.33 mm; Metered dose: a50 µg, b250 µg

Figure 1. Effect of total non-volatile component on MMAD (µm) of BDP pMDI solution formulations in HFA 134a. Data derived from Table 1.

Figure 2. Relationship between experimental and theoretical MMAD values using Equation 3 and experimental data from Table 1.
deviation. With the larger orifices, more coarse particles are formed which broadens the distribution and moves its mean to higher values.

Actuator orifice size has a greater influence on plume maximum velocity and duration. Over the range studied, the maximum velocity of the plume measured at a distance of 4 cm from its origin decreased from 7.15 m sec\(^{-1}\) with the largest orifice to 5.12 m sec\(^{-1}\) for the smallest. Correspondingly, the plume duration increased from 0.18 sec to 1.16 sec (Figure 4).

The use of smaller apertures producing slower clouds over a longer period should facilitate the co-ordination of cloud generation and the patient's inspiration.

### THE EFFECT OF METERED VOLUME AND PROPELLANT VAPOUR PRESSURE

Although the effect of metered volume and choice of propellant is less pronounced, useful modulating effects can be obtained. Valves commonly meter volumes from 25 to 100 µl allowing a degree of freedom in the amount of drug and non-volatile component which can be delivered.

HFA 134a and HFA 227 differ significantly in vapour pressure; 570 and 390 kPa at 20° respectively. Addition of co-solvent and non-volatile additive lowers the propellant vapour and pack pressures, although those for HFA 134a systems remain higher than for equivalent HFA 227 systems. Brambilla et al. (2) showed that a BDP/ethanol/glycerol combination in a high pack pressure HFA 134a formulation (550 kPa at 20°) gave a cloud with an MMAD of 2.8 µm compared with 3.5 µm when HFA 227 is used (pack pressure at 20° = 350 kPa). Similar effects were obtained with formulations containing budesonide and ipratropium bromide. In all cases, higher pressures lead to more efficient atomization and finer sprays. However, unlike the effect of actuator orifice, there was little associated change in fine particle dose.

### THE FORMULATION OF BDP USING HFA

Although the principles of Modulite® permit the development of highly efficient formulations to target particular parts of the lungs, an immediate opportunity arises with the replacement of CFC with HFA in existing...
Figure 4. Effect of actuator orifice on the plume maximum velocity and plume duration for a formulation containing 1.3% w/w glycerol and 15% w/w ethanol.

Figure 5. Phase diagram for BDP (250 µg/50 µl) and (1.3 ± 0.1)% w/w glycerol system, demonstrating the miscibility of BDP, HFA 134a, absolute ethanol, and water (T = 0–20°C).

formulations. Generally, the CFC formulations are far from optimum and in many cases very inefficient, depositing only a tiny fraction at the site of action. Nevertheless, they are widely used with well-established dose regimens. Replacement poses a dilemma. Modulite® could be used to make a highly efficient
product. However, when Leach et al. (3) devised the QVAR® solution formulation of BDP with a much reduced MMAD of 1.1 μm, the effective dose was more than halved and a complex dose conversion was required (4).

The alternative is to use Modulite® to match the properties of existing products, maintaining established dose schedules and promoting a seamless transition.

In using Modulite® to match existing products, solubility studies to establish likely formulations containing BDP, the chosen HFA, ethanol and small amounts of water were first performed. Formulations were assessed visually in special glass containers and a phase diagram created which displays the regions in which combinations of HFA 134a, ethanol and water will dissolve 0.424% w/w BDP to give a single phase (Figure 5).

Water was added to establish the tolerance of the formulations to ingress which arises from absorption during processing and storage.

This data was allied to the inclusion of non-volatile components and the selection of aperture orifices, assessed using the in-vitro model described above and exemplified in Tables 1 and 2.

Selection was made by permuting variables to give the closest match to the comparator formulation. When a formulation containing 0.085% w/w BDP, 1.3% w/w glycerol and 13% w/w ethanol in HFA134a was equipped with a Bespak BK357 valve, the particle size distribution given in Figure 6 was obtained.

Data for a comparator CFC suspension formula (Becotide®, 50, Allen and Hanbury) and a simple solution formula (Qvar®, 50, 3M) are also given. It is immediately apparent that Qvar® produces a very fine particle cloud with large amounts of the dose as particles less than 2 μm. The match between Modulite® and Becotide® is very much closer. It is not, however, perfect because the physical mechanisms in the atomisation of suspensions and solutions will differ. However, in the therapeutically useful range 1.1–4.7 μm, the Modulite® formulation gives a value of 1.1 μg compared with 10.3 μg for Becotide®. The HFA formulation has marginally more fine particles below 1 μm, depressing the MMAD from Becotide®'s 3.4 μm to 2.9 μm. Nevertheless, physical characteristics are such that a product close to being pharmaceutically equivalent can be claimed. Differences in clinical performance are, therefore, unlikely and simple substitution can be made without change of dose or regimen.

CONCLUSIONS

The principles of Modulite® permute two major variables – the non-volatile content of a solution formula and the actuator orifice geometry – and two minor variables – metered volume and vapour pressure of the propellant – to design aerosols with chosen particle size and plume speed. This facilitates co-ordination of dose generation with inspiration and provides a mechanism for targeting drug delivery to different parts of the lung. The principles are powerfully exemplified by designing a HFA-propelled beclometasone dipropionate product which closely matches an existing product which uses chlorofluorocarbons.

REFERENCES