Introduction

Modulite®: simplifying the changeover

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Respiratory delivery is at present the normal route of administration of drugs for respiratory diseases, and this is accomplished by the use of a variety of devices such as metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulizers, all of which have their place in treatment.

Nearly 80% of asthmatic patients worldwide use MDIs. Their popularity is due to a number of factors. They are small, portable and easy-to-use devices. Furthermore, the design of all types of MDIs is similar. Hence there is a familiarity and usually less need for education compared with DPIs where each company produces a unique design with varying operating principles and instructions.

Dose consistency of MDIs is good with the energy for delivering the dose being constant (the evaporating propellant) unlike DPIs where the dose may vary with the patient’s inspiratory flow effort.

Chlorofluorohydrocarbons (CFCs) have been used widely in many products of the industrialized world (general aerosols, e.g. hairsprays, toiletries, etc; refrigeration, plastics); they are also used in MDIs and other types of pharmaceutical aerosol. Their discharge into the atmosphere has led to a depletion of the ozone levels with consequent environmental threats. The Montreal Protocol was drafted by the United Nations Environmental Programme in 1987 in response to the alarming situation. Production of CFCs was halted in the developed world in 1996 except for ‘essential users’ which include MDIs. Efforts to eliminate the need for CFCs even in these ‘essential’ applications have continued and the European Commission, in its document Strategy for the Phase-Out of CFCs in Metered Dose Inhalers [COM (1998) 603 Final] published on 23 October 1998, has set a target date of 2005 for the withdrawal of CFC-based inhalers.

The search for new and ‘ozone friendly’ propellants covered a number of alternatives such as hydrocarbons (butane, pentane) but soon concentrated on two hydrofluoroalkanes (HFAs), first HFA 134a and then HFA 227. They have suitable physicochemical properties which are similar to the CFCs they replace.

Major formulation changes were needed and in many cases the only common ingredient between CFC and HFA products is the drug, with all excipients being changed. CFCs and HFAs share a number of basic technical characteristics but differ in such physical properties as density, vapour pressure, molecular polarity and evaporation kinetics. These differences have necessitated the development of new formulations, valves and manufacturing processes for HFA 134a inhalers.

The reformulation of CFC MDIs with ozone-friendly propellants (HFAs) has proved much more difficult than originally envisaged and the pharmaceutical industry is still investing significant resources in the development of the new generation MDIs.

Modulite® has been developed by the Chiesi Group to solve the technical problems associated with the phase-out of CFCs and their replacement with HFAs. Key advantages of the Modulite® technology are stable and uniform dose delivery of HFA-based formulations and flexibility in tailoring the particle size distribution of the cloud generated on actuation of the MDI.

Particle size is a critical factor in aerosolized drug delivery, affecting both the dose quantity and delivery site, and hence clinical efficacy and tolerability. Different regions of the lungs can be targeted modulating the dimension of the particles.

This principle can be applied to HFA formulations in two ways:

- It is possible to generate clouds closely matching particle size and drug mass of current CFC suspension formulations (seamless transition),
- Formulation can be refined to remove unwanted cloud components: i.e. products with a reduced nominal dose and a larger percentage (70–80%) of clinically useful product and with defined particle size targeting specific lung areas.

Modulite® HFA technology allows an easy transition to CFC-free products and may also be exploited to improve the performance of MDIs or develop new formulations with original cloud characteristics according to the
clinical profile of the drug to be administered. It can be envisaged that in the future, Modulite® HFA technology may also be applied to the delivery via the lungs of non-pulmonary drugs.

The first practical result of the application of the Modulite® technology to pharmaceuticals are new formulations of beclomethasone dipropionate (BDP) with HFA 134a. The development programme has covered four products containing 50 μg, 100 μg, 200 μg or 250 μg per actuation of BDP in inhalers delivering 200 actuations. The products have been designed to be equivalent in terms of efficacy, safety and dose delivered to currently marketed CFC-containing inhalers that provide the same amount of BDP per actuation, so as to allow seamless transition to CFC-free MDI treatment, minimizing anxiety and concerns in patients and their families when changing their current asthma medications based on CFC.

This supplement of Respiratory Medicine presents an overview of the technical and clinical aspects of the Modulite® technology.

In the first paper D. Ganderton et al. explain how Modulite® has been developed taking advantage of the phasing-out of CFC MDIs to design a new and improved MDI. The emission of clouds of particles with a chosen size and plume speed with Modulite® was possible by the addition of glycerol as a non-volatile excipient to the formulation and by modifying the geometry of the actuator orifice. The practical result is that Modulite® generates clouds closely matching particle size and drug mass of current CFC formulations, thus maintaining established dose schedules and promoting a 'seamless transition'.

In the second paper, A. Woodcock et al. illustrate the pharmacokinetic and pharmacodynamic characteristics of Modulite®. Studies conducted in healthy volunteers, as well as in asthmatic patients, demonstrate that BDP and budesonide Modulite® did not produce significantly different effects on serum cortisol or urinary cortisol excretion at high daily doses, compared with the CFC products. Also, the systemic exposure measured by plasma levels of B16MP, the active metabolite of BDP, was comparable between BDP Modulite® and BDP-CFC and was substantially less than that obtained with a different, extrafine HFA formulation of BDP. These studies confirm that BDP Modulite® can replace the old BDP-CFC without the need to change the daily dose of inhaled drug.

The opportunity offered by BDP Modulite® to replace the BDP-CFC without the necessity to adjust patient's dosing schedule was proved in five clinical studies involving 1158 asthmatic patients, both adults and children and with different grades of disease severity. J. Bousquet and L. Cantini review those studies in the last paper of this review. Studies were conducted comparing BDP Modulite® with BDP-CFC and demonstrated similarity of efficacy on the main variables of assessment. The safety of the new BDP Modulite® was also equivalent to that of the CFC-based product.

The results of the development programme demonstrate that Modulite® represents a good opportunity in this period of change from the traditional MDIs to new and improved HFA MDIs.