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CONTENTS

Development of a pMDI Formulation Containing Budesonide

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A hydrofluoroalkane (HFA) based budesonide formulation was developed so that 220 µg of budesonide per shot would exit the valve over 200 doses. This formulation was designed to be physically and chemically stable and it would give reproducible aerosol performances[1-4]. The stability of the resulting metered dose inhaler was also evaluated under accelerated storage conditions (40°/75%RH) up to 6 mo. The aim was also to match the innovator Pulmicort® CFC (chlorofluorocarbon) product in terms of *in vitro* performances.

MATERIALS AND METHODS

Excipients selected for evaluation were polyethylene glycol 300 (at levels of 0.15 to 5% w/w, supplied by Fluka, France) and ethanol (at levels of 0.2 to 2% w/w, supplied by Prolabo, France)[4]. The amount of micronised budesonide (supplied by Aarti Healthcare Ltd, India) introduced into the formulation vessel was such that the appropriate dose of budesonide would be delivered to the patient. Pressurised metered dose inhalers (pMDIs) were prepared by introducing the HFA budesonide suspension formulation as a one step filling process, through a metering valve previously crimped onto a standard anodised aluminium canister (supplied by Presspart, Great-Britain).

To evaluate the homogeneity of the dispersion by visual inspection, formulations were filled into glass bottles. Promising formulations were evaluated with regard to drug stability upon storage, delivered dose uniformity (DDU) over 10 actuations at 28.3 l/min and particle size distribution using a Next Generation Impactor at 30 l/min.

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Valve types and materials combined with various actuator outlet orifice diameters were also evaluated. A first set of results was obtained with a DF30/50 RCU valve having polyacetal plastic components and nitrile rubber and thermoplastic elastomer gaskets combined with a 0.7 mm outlet orifice diameter actuator. A second set of results was obtained with a DF316/50 RCU valve with polyacetal plastic components and nitrile rubber and thermoplastic elastomer gaskets combined with a 0.5 mm outlet orifice diameter actuator.

RESULTS AND DISCUSSION

DDU results obtained with a DF30/50 valve fitted with a 0.7 mm outlet orifice diameter actuator are shown in (fig. 1) and those obtained with a DF316/50 valve fitted with a 0.5 mm outlet orifice diameter actuator are shown in (fig. 2). DDU data is summarised in Table 1 and conforms to the current FDA MDI/DPI guidance document for Dose Uniformity. Fine Particle Fraction (FPF) results are summarised in Table 2.

During this study, PEG 300 at levels less than 0.5% w/w was found to ensure good product performances and valve functioning throughout the MDI units' life. There was no sign of valve sticking. Ethanol at levels less than 1% w/w helped dissolution of the PEG300 without causing significant solubilisation of budesonide, which could lead to problems of chemical degradation. The level of ethanol selected also helped to decrease the propensity for rapid formation of coarse flocks. This formulation was readily re-dispersible and avoided irreproducible dosing of the drug. The stable suspension of particulate budesonide was aided by employing a mixture of HFA propellants closely matching the density of the micronised budesonide.

Valois offers a fully developed budesonide HFA formulation. It includes a suspension formulation stable for at least 6 mo under 40°/75%RH storage conditions, together with the selected appropriate valve, canister and actuator.

TABLE 1: DELIVERED DOSE UNIFORMITY THROUGH CAN LIFE DEPENDING ON USED VALVE TYPE AND OUTLET ORIFICE SIZE OF THE ACTUATOR

	DF30 valve (n=10) 0.7 mm actuator	DF316 valve (n=2) 0.5 mm actuator
T0	217±22 µg	208±23 µg
T3 (40°/75%RH)	223±25 µg	223±20 µg
T6 (40°/75%RH)	218±15 µg	Not determined

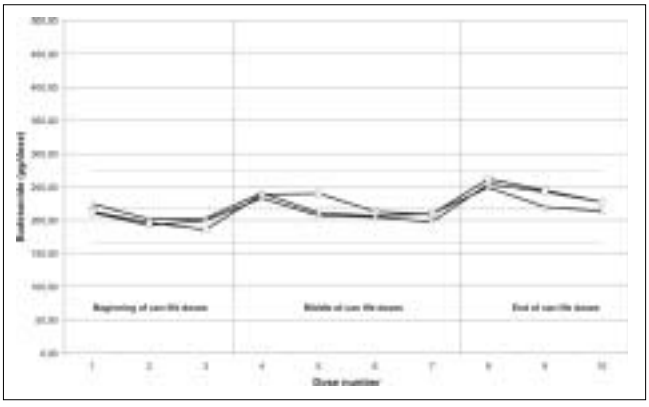

Fig. 1: Delivered dose uniformity of the formulations with DF30/50 valve
Delivered dose uniformity of the formulations at T 0 (—◊—), T 3 mo (—□—) and T 6 mo (—Δ—) under accelerated storage conditions using a 0.7 mm actuator fitted on a DF30/50 valve

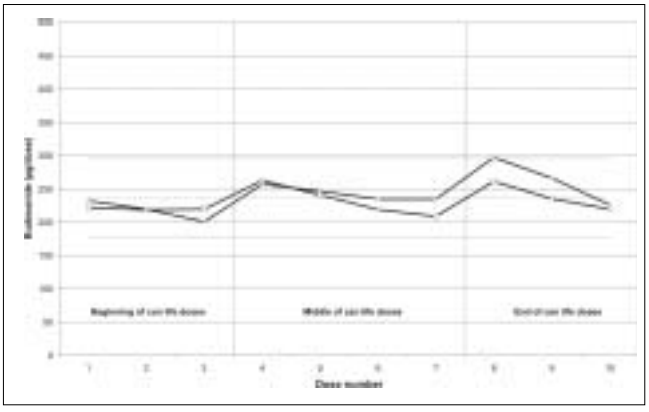

Fig. 2: Delivered dose uniformity of the formulation with a DF316/50 valve
Delivered dose uniformity of the formulation at T 0 (—□—) and T 3 mo under accelerated storage conditions (—◊—) using a 0.5 mm actuator fitted on a DF316/50 valve

TABLE 2: AERODYNAMIC PARTICLE SIZE DISTRIBUTION DEPENDING ON USED VALVE TYPE AND OUTLET ORIFICE SIZE OF THE ACTUATOR

	DF30 valve (n=3) 0.7 mm actuator		DF316 valve (n=2) 0.5 mm actuator		Pulmicort CFC (n=3) as supplied actuator	
	FPF (%)	MMAD (µm)	FPF (%)	MMAD (µm)	FPF (%)	MMAD (µm)
T0	17±2	5.06±0.02	19±2	5.06±0.05	14±1	5.46±0.11
T3 (40°/75%RH)	16±1	5.28±0.03	18±1	5.29±0.11	Not determined	
T6 (40°/75%RH)	14±2	5.36±0.04	Not determined		Not determined	

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