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Development of a pMDI Formulation Containing Salbutamol

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A hydrofluoroalkane (HFA) based salbutamol formulation was developed so that 120 µg of salbutamol sulphate per shot would exit the valve over 200 doses. This formulation was designed to be physically stable upon visual observation and it would give reproducible aerosol performances1-3. The stability of the resulting metered dose inhaler was also evaluated under accelerated storage conditions (40°/75%RH) up to 6 mo on a small scale and up to 3 mo on a larger scale batch. The aim was also to match the innovative Ventolin® HFA 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). The pressurised metered dose inhalers (pMDIs) were prepared on a laboratory scale by a two step filling process: introduction of the drug in each canister, crimping of the metering valve onto a standard anodised aluminium canister (supplied by Presspart, Great-Britain) and filling of propellant through the valve. Other pMDIs were prepared as a one step filling process by introducing the HFA salbutamol suspension formulation through a metering valve previously crimped onto a canister.

Formulations were evaluated with regard to drug stability upon storage, delivered dose uniformity (DDU) over 10 actuations at 28.3 l/min. Combinations of different formulations together with different valve configurations were tested with 0.5 mm outlet orifice diameter actuators.

RESULTS AND DISCUSSION

Delivered dose uniformity results obtained on a laboratory scale (two step filling process, n= 3) can be found in figs. 1 to 3. Delivered dose uniformity results

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Fig. 1: Delivered dose uniformity of formulation C using valve configuration C1 at T 0 (–◊–), T 1 (–□–), T 3 (–○–) and T 6 mo (–∆–) under accelerated storage conditions; two step filling
obtained on a larger scale (one step filling process, n=10) can be found in figs. 4 to 6.

A mixture of HFA propellants closely matching the density of the micronised salbutamol has been used to improve the suspension stability. The formulation is readily re-dispersible, and upon re-dispersion, does not flocculate quickly and so prevents irregular dosing of the drug. However, addition of excipients alters the inter particulates forces as well as interaction between the formulation and the valve components. Changes in DDU performances are then seen.

Valois offers a fully developed salbutamol HFA formulation. It has good DDU stability for at least 6 mo under 40°/75% RH storage conditions, together with the selected appropriate valve, canister and actuator.

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Several mechanisms that lead to in situ gel formation namely, solvent exchange, UV-irradiation, ionic cross-linkage, pH change, and temperature modulation have been reported for design of drug delivery systems. Herewith we have investigated a novel approach Aqua-triggered In Situ (ATIS) gel formation wherein water acts as the trigger for gelling. Zolmitriptan (ZLT) a potent antimigraine agent exhibits low (40%) oral bioavailability. Nasal drug delivery system of ZLT could provide the dual advantage of enhanced bioavailability with rapid onset of action. The objective of the present work was the design and evaluation of ATIS gel formation in the design of in situ gelling microemulsion (ME) based nasal sprays of ZLT.

MATERIALS AND METHODS

The chemicals were received as gift from BASF India Ltd., Abitec Corporation, USA, and Zolmitriptan (Cipla India Ltd).

Construction of pseudo ternary phase diagram:
Pseudo-ternary phase diagrams were constructed using water titration method at ambient temperature (25°C) to determine the ME regions and gelling regions. PVD-O was selected as oil phase, PVD-S as surfactant and PVD-CoS as co-surfactant. The weight ratios of PVD-S to PVD-CoS were varied from 1:1, 2:1, 3:1 and 4:1, respectively. The ME region and ME gel region were identified.

Preparation of microemulsion for ATIS gel formation:
ZLT and excipient were dissolved in water, surfactant, and co-surfactant mixture and mixed with oil. The concentration of surfactant, co-surfactant and water were fine tuned to obtain sprayable ME which exhibit ATIS gel formation.

Characterization of ATIS gel:
Drug content was monitored by UV spectroscopy at 284 nm. ATIS gelling was determined by spraying the ME using VP 50 spray nozzle on an artificial mucin film supported on a filter paper. The resistance of the sample to flow was monitored by holding the mucin film at 180° facing downwards. The ME (colored with a dye) were sprayed using the Valois VP 50 µl nozzle on white filter paper to assess the spray pattern. The Beckman Coulter N4plus particle size analyzer was used for globule size determination. The effect of pH on ME formulations for ATIS Gel formation was evaluated at different pH (5-7) and SMEDDS as control. Bioadhesion was evaluated by a modified balance method designed in house.

RESULTS AND DISCUSSION

MEs are known to exhibit gel formation under certain conditions. ATIS gel formulation is based on design of sprayable ME at the phase boundary of the gel region such that further contact with water (aqua) triggered gel formation. Accordingly ZLT loaded ME were prepared by selecting appropriate concentrations of ME components. Pseudo ternary