CONTENTS

REVIEW ARTICLES

Recent Trends in Drug-Likeness Prediction: A Comprehensive Review of In Silico Methods
R. U. KADAM AND N. ROY 609-615

Biodegradable Polymers: Which, When and Why?
V. B. KOTWAL, MARIA SAIFEE, NAZMA INAMDAR AND KIRAN BHISE 616-625

RESEARCH PAPERS

Strong Cation Exchange Resin for Improving Physicochemical Properties and Sustaining Release of Ranitidine Hydrochloride
S. KHAN, A. GAUHA, P. BHATLO, AND P. K. KATARIYA 626-632

Novel Co-Processed Excipients of Mannitol and Microcrystalline Cellulose for Preparing Fast Dissolving Tablets of Glipizide
S. JACOB, A. A. SHIRWAIKAR, A. JOSEPH, K. K. SRINIVASAN 633-639

Formulation and Optimization of Directly Compressible Isosiazid Modified Release Matrix Tablet
M. C. GOHEL, R. K. PARIKH, M. N. PADSHALA, K. G. SARVAYA AND D. G. JENA 640-645

Effect of Casting Solvent and Polymer on Permeability of Propranolol Hydrochloride Through Membrane Controlled Transdermal Drug Delivery System
T. E. G. K. MURTHY AND V. S. KISHORE 646-650

Preparation of Mucoadhesive Microspheres for Nasal Delivery by Spray Drying
MAHALAXMI RATHANANAND, D. S. KUMAR, A. SHIRWAIKAR, RAVI KUMAR, D. SAMPATH KUMAR AND R. S. PRASAD 651-657

Effect of Polymers on Crystallo-co-agglomeration of Ibuprofen-Paracetamol: Factorial Design

Synthesis and Antimicrobial Evaluation of Some Novel 2-imino-3-(4-carboxamido pyridyl)-5-Arylidene-4-Thiazolidinones and their Brominated Derivatives
P. MISHRA, T. LUKOSE AND S. K. KASHAW 665-668

Measurement of Urine and Plasma Oxalate with Reusable Strip of Amaranthus Leaf Oxalate Oxidase
NISHA SHARMA, MINAKSHI SHARMA, V. KUMAR AND C. S. PUNDIR 669-673

SHORT COMMUNICATIONS

Simultaneous HPLC Estimation of Omeprazole and Domperidone from Tablets
LAKSHMI SVASUBLABHANIAN AND V. ANILKUMAR 674-676

Isolation and Evaluation of Fenugreek Seed Husk as a Granulating Agent
AMELIA AVACHAT, K. N. GUJAR, V. B. KOTWAL AND SONALI PATIL 676-679

Synthesis and In Vitro Efficacy of some Halogenated Imine Derivatives as Potential Antimicrobial Agents
A. K. HALVE, DEEPTI BHADAURIA, B. BHASKAR, R. DUBEY AND VASUDHA SHARMA 680-682

Simultaneous Spectrophotometric Estimation of Atorvastatin Calcium and Ezetimibe in Tablets
S. S. SONAWANE, A. A. SHIRKEDKAR, R. A. FURSULE AND S. J. SURANA 683-684

High Performance Thin Layer Chromatographic Estimation of Lansoprazole and Domperidone in Tablets
J. V. SUSHEEL, M. LEKHA AND T. K. RAVI 684-686

Antimicrobial Activity of Helicteres isora Root
S. VENKATESH, K. SAILAXMI, B. MADHAVA REDDY AND MULLANGI RAMESH 687-689

Synthesis and Antibacterial Activity of 2-phenyl-3,5-diphenyl (substituted) -6-aryl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazoles

Simultaneous Estimation of Aceclofenac, Paracetamol and Chlorzoxazone in Tablets
G. GARG, SWARNALATA SARAF AND S. SARAF 692-694

Reverse Phase High Performance Liquid Chromatography Method for Estimation of Ezetimibe in Bulk and Pharmaceutical Formulations
S. K. AKMAR, LATA KOTHAPALLI, ASHA THOMAS, SUMITRA JANGAM AND A. D. DESHPANDE 695-697

Synthesis and Antiinflammatory Activity of N-Aryl Anthranilic Acid and its Derivatives

RP-HPLC Method for the Determination of Atorvastatin calcium and Nicotinic acid in Combined Tablet Dosage Form
D. A. SHAH, K. K. BHATT, R. S. MEHTA, M. B. SHANKAR AND S. L. BALDANA 700-703

Determination of Etoricoxib in Pharmaceutical Formulations by HPLC Method
H. M. PATEL, B. N. SUHAGIA, S. A. SHAH AND I. S. RATHOD 703-705

Proceedings of the Symposium on Advances in Pulmonary and Nasal Drug Delivery, October 2007, Mumbai

Albumin Microspheres of Fluticasone Propionate Inclusion Complexes for Pulmonary Delivery

Design and Development of Thermoreversible Mucoadhesive Microemulsion for Intranasal Delivery of Sumatriptan Succinate
R. S. BHANUSHALI AND A. N. BAJAJ 709-712

Preparation and Characterization of Chitosan Nanoparticles for Nose to Brain Delivery of a Cholinesterase inhibitor
BHAVNA, V. SHARMA, M. ALI, S. BABOOTA AND J. ALI 712-713

Poloxamer Coated Fluticasone Propionate Microparticles for Pulmonary Delivery; In Vivo Lung Deposition and Efficacy Studies

Sustained Release Budesonide Liposomes: Lung Deposition and Efficacy Evaluation

Generation of Budesonide Microparticles by Spray Drying Technology for Pulmonary Delivery
S. R. NAIKWADE AND A. N. BAJAJ 717-721

Microemulsion of Lamotrigine for Nasal Delivery
A. U. SHENDE, R. R. PATIL AND P. V. DEVARAJAN 721-722

Development of a pmDI Formulation Containing Budesonide
E. ROBINS, G. BROUET AND S. PRIOLKAR 722-724

Development of a pmDI Formulation Containing Salbutamol
E. ROBINS, G. WILLIAMS AND S. PRIOLKAR 724-726

Aqua Triggered In Situ Gelling Microemulsion for Nasal Delivery
R. R. SHELKE AND P. V. DEVARAJAN 726-727

In vivo Performance of Nasal Spray Pumps in Human Volunteers By SPECT-CT Imaging
S. A. HAZARE, M. D. MENON, P. S. SONI, G. WILLIAMS AND G. BROUET 728-729

Nasal Permeation Enhancement of Sumatriptan Succinate through Nasal Mucosa
S. S. SHIDHAYE, N. S. SAINDANE, P. V. THAKKAR, S. B. SUTAR AND V. J. KADAM 729-731

Formulation Development of Eucalyptus Oil Microemulsion for Intranasal Delivery
N. G. TIWARI AND A. N. BAJAJ 731-733
increase in concentration of the oil phase irrespective of solubility in oil.

Solubilization capacity of ME of lamotrigine was significantly lower than predicted. Moreover no appreciable difference was seen in solubilization capacity of MI and ME formulation. This observation though contrary to our previous study with tamoxifen, where marked increase in solubilization was observed, was in accordance with reports on steroid ME3. Though the oil phase is known to play a significant role in generation of the interface it may not always play a major role in drug solubilization. Moreover, cosurfactants may affect the micelle structure3 thereby causing significant reduction in solubilization by MI and ME despite high solubility of drug in cosurfactant. The decreased solubilization of lamotrigine by ME compared to the predicted could be due to interaction of the drug with ME components. This however needs to be explored and confirmed. However adequate solubilization was observed to enable design of ME [5 mg lamotrigine per actuation (100 μl)] for nasal delivery.

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Development of a pMDI Formulation Containing Budesonide

E. ROBINS*, G. BROUET AND S. PRIOLKAR
Direction Technique, Valois SAS, Route des Falaises, 27100 Le Vaudreuil, France

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 performances1-4. 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)5. 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.
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

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

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

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

The authors would like to thank Presspart for supplying the canisters.

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Development of a pMDI Formulation Containing Salbutamol

E. ROBINS*, G. WILLIAMS AND S. PRIOLKAR
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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 performances\textsuperscript{1-3}. 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\textsuperscript{®} HFA product in terms of \textit{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