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A COMPARATIVE EVALUATION OF FORMOTEROL-BASED MARKETED INHALED MEDICINES THROUGHOUT THE DEVICE LIFE, FOCUSING ON INSPIRATORY AIRFLOW AND HIGH TEMPERATURE AND HUMIDITY USE CONDITIONS

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PURPOSE

The success of inhalation therapy depends on the patient, the device and the formulation.

Indeed, the ideal inhalation medicine has to present an accurate and consistent drug delivery as well as features that improve the device handling and preference by the patients [1,2]. An ideal device has to deliver an accurate delivered dose (DD) and fine particle dose (FPD) throughout the device life, with low dependency on the patient's inspiratory airflows and with the use of the medicine at different temperature and humidity conditions. In this study, a comparative evaluation was performed on 5 formoterol-based marketed inhaled medicines currently used for maintenance treatment of asthma and chronic obstructive pulmonary disease :

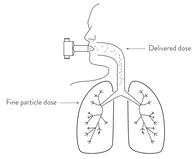
- 2 capsule-based dry powder inhalers (DPIs) : Foradil® from Novartis and Formagal® from SMB,
- 2 reservoir-based DPIs : Oxis® from AstraZeneca and Novolizer® from Meda, and
- 1 pressurized metered dose inhaler (pMDI) : Formoair® from Chiesi.

METHODS

		Foradil®	Formagal®	Oxis®	Novolizer®	Formoair®
	Inhaled medicine					
Device	Inhalation device	Aerolizer® DPI 4 pins	Axahaler® DPI 1 pin	Turbohaler® DPI	Novolizer® DPI	pMDI
	Type (number of doses)	Monodose (60)	Monodose (60)	Monodose (60)	Multidose (60)	Multidose (100)
	Dose container	Hard-gelatine capsules in blister	HPMC capsules in desiccant container	Reservoir	Cartridge	Pressurized reservoir
Formulation	Formoterol fumarate dihydrate	12 µg (nominal)	12 µg (nominal) ➡ 9 µg emitted	12 µg (nominal) ➡ 9 µg emitted	12 µg (nominal) ➡ 10.2 µg emitted	12 µg (nominal) ➡ 10.1 µg emitted
	Formulation	Lactose carrier blend	Lactose carrier blend	Fine lactose aggregates	Lactose carrier blend	Propellant solution
	Excipient	Sieved 150-mesh Lactose (<100 µm) ➡ < 500 µg emitted	16.8 mg anhydrous lactose 12.6 mg emitted and 7.2 mg Lactose ➡ 5.4 mg emitted	588 µg Lactose ➡ 441 µg emitted	Lactose monohydrate	Norflurane (HFA134a), anhydrous ethanol, hydrochloric acid
	Company	Novartis	SMB	Astra Zeneca	Meda	Chiesi

DEVICE HANDLING

DRUG DELIVERY

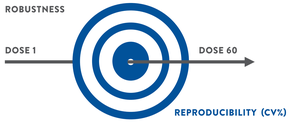


The device handling was evaluated in terms of (i) the number of steps and dexterity required for each step for the priming, the dose loading, the inhalation and the cleaning, (ii) the feedback to the user on dose delivery, and (iii) the device resistance to the airflow.

Then, the DD and the FPD were evaluated in terms of their reproducibility (CV%) and robustness throughout the device life (at the beginning, middle and end), different inspiratory airflows (30 L/min, 60 L/min, 100 L/min and/or the airflow for a pressure drop of 4 kPa through the DPI) and by simulating the use of the medicines at high temperature and humidity conditions (i.e. 4 h at 40°C 75% relative humidity) on a DPI loaded with a dose. The DDs were determined on doses 2, 3, 16, 17, 30, 31, 44, 45, 58 and 59 using the test recommended by United States Pharmacopeia (USP). The FPDs were determined after in vitro deposition in a USP apparatus 5 (i.e. the Next Generation Impactor) using the test recommended by USP and using doses 5-14, 19-28, 33-42 and 47-56.

RESULTS ON DRUG DELIVERY

THROUGHOUT DEVICE LIFE

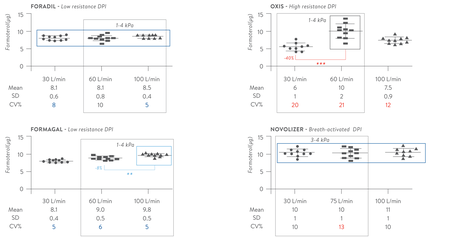


	Foradil	Formagal	Oxis	Novolizer	Formoair
Induction port (%)	13 ± 2	7.3 ± 0.5	15 ± 2	20 ± 3	43 ± 1
MMAD (µm)	3.25 ± 0.07	3.15 ± 0.08	1.95 ± 0.10	1.56 ± 0.06	0.68 ± 0.02
DD (µg) Reproducibility Robustness	9.3 ± 0.4 5% NS	9.6 ± 0.7 7% NS	9.7 ± 1.9 20% S	9.5 ± 1.1 11% S	9.9 ± 0.5 5% NS
FPD (µg) Reproducibility Robustness	3.2 ± 0.2 6% NS	3.2 ± 0.1 4% S	4.0 ± 0.5 12% NS	3.0 ± 0.1 4% NS	3.5 ± 0.2 7% NS

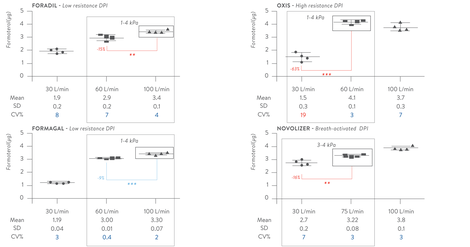
Optimal for formoteral delivery — Moderate for formoteral delivery — Unsatisfactory for formoteral delivery

PATIENT'S INSPIRATORY AIRFLOWS

Delivered Doses

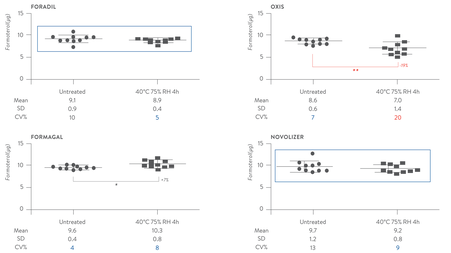


Fine Particle Doses

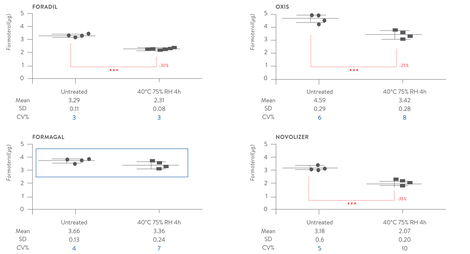


HIGH TEMPERATURE AND HUMIDITY USE CONDITIONS

Delivered Doses



Fine Particle Doses



RESULTS ON DEVICE HANDLING

	Foradil	Formagal	Oxis	Novolizer	Formoair
Priming steps	0	0	1	4	1
Dose loading steps	6	6	3	3	1
Inhalation steps	5	5	5	5	5
Cleaning steps	4	4	2	2(+8*)	2(+4*)
Dexterity	High	High	Low	Medium	High
Feedback	Visual, Auditory, Taste		(Taste)	Visual, (Auditory), Taste	Cold and high velocity plume
Airflow (Resistance)	100 L/min (Low)	100 L/min (Low)	57 L/min (High)	75 L/min (Medium)	/

Easy for patient use — Normal for patient use — Difficul for patient use

GENERAL CONCLUSIONS

pMDI in comparison to DPIs showed as main disadvantages the hand-mouth coordination requiring high dexterity, the highest deposition in the induction port simulating the throat and in peripheral lung where there are few smooth muscles.

Reservoir-based DPIs in comparison to capsule-based DPIs presented priming steps, higher resistance devices, lower feedback (depending on the device) and lower reproducibility and robustness of drug delivery throughout device life (in terms of DD), different inspiratory airflow and at high temperature and humidity use condition, especially for the Oxis.

–Therefore, capsule-based DPIs showed, overall, better accurate, reproducible and consistent drug delivery throughout device life, different inspiratory airflow and at high temperature and humidity use condition, especially for the Formagal. However, some features for the device handling, such as lower dose loading and cleaning steps, could be improved.

FUNDING

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2. Chrystyn, H., Int J Clin Pract 2007, 61(6):1022-36