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PRESCRIPTION DIVISION

DETERMINATION OF VOLATILE ORGANIC COMPOUNDS FROM THE PROHALER® DRY POWDER INHALER

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SUMMARY / INTRODUCTION

Dry Powder Inhalers (DPI) need to be fully characterized in terms of leachables and extractables as these could potentially migrate from the device materials to the powder formulation. In addition these compounds could either interact with the formulation and degrade it, or be harmful to the patient. This work describes a method developed to recover and quantify volatile organic compounds, which could potentially be inhaled by a patient, from a dry powder inhaler device. The Prohaler® DPI device from Aptar used in this study is a multi unit dose dry powder device where drug doses are stored in an aluminium blister strip. The materials of construction include ABS, polypropylene, polyacetal and silicone elastomer.

Specific test equipment was designed to connect a cartridge to the Prohaler® device and to a vacuum pump, so that air is circulated through the device and then through the cartridge. Any volatile compounds are then adsorbed onto the cartridge which can then be de-sorbed chemically or thermally and analysed by HPLC or GC. Since the device contains no powder formulation, only the compounds coming from the device plastic/rubber/metallic components are investigated here. The levels obtained in extreme conditions compared to reality will then be compared to Safety Concern Thresholds typically accepted for inhalation products[1].

MATERIALS AND METHODS

- Specific testing system designed for this study: the dry powder device is connected to a pump and a cartridge containing either active carbon phase or silica with DNPH (DiNitroPhenylHydrazine) reagent phase, as described in Image 1. The volatile compounds are then passed through the cartridge and adsorbed on the phase.
- Test conditions: room temperature and 40°C/75% RH.
- Inhaled air volume: 240 litres (since up to 30 doses can be taken by a patient with a typical inhalation volume of 4 litres for each dose,[3] a total inhalation volume of 120 litres will be inhaled. A safety multiple of 2 was used).
- Aspiration flow rate 0.5 litre per minute (the organic layer phases contained in the different cartridges cannot support the pressure drop caused by higher flow rates. Also, higher aspiration flow rates would not allow volatile organic species to be adsorbed on the active carbon or silica phase).
- Analytical technique: thermal or chemical de-sorption followed by analysis on gas chromatography coupled with mass detection (GCMS) or on high performance liquid chromatography (HPLC) coupled with UV (ultraviolet) detection. Normalized methods NFX 43-267 (GC/MS), NFX 43-264 (HPLC/UV) and semi-quantitative suitably validated methods were used.
- Three blanks and three replicates were carried out for each experimental condition.
- Cartridges: SKC Sorbent tube, silica+DNPH, 6 x 110mm, for formaldehyde, Marker Mi active carbonized molecular sieves, 6 x 88mm, for other organic volatile compounds
- Pump: Escort Elf air sampling Supelco, range 0.5 – 3.0lpm

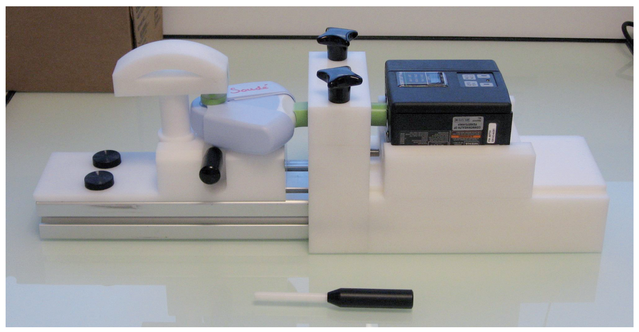

Image 1. Experimental Testing System

RESULTS

LOQ – limit of quantification
(1) without blister strip (2) with blister strip
(3) semi-quantitative results (4) Normalized quantitative results

sample	Hexamethyl disiloxane ng/cartridge (3)	Methyl-6, 5-hepten-2-one ng/cartridge (3)	Nonaldehyde ng/cartridge (3)	Dodecane ng/cartridge (4)	LOQ ng/cartridge
blank 1 40°C	<10	<10	<10	<10	10
blank 2 40°C	80	<10	<10	<10	10
blank 3 40°C	<10	<10	<10	60	10
sample 1 40°C (1)	**410**	<10	<10	**260**	10
sample 2 40°C (1)	**450**	<10	<10	**290**	10
sample 3 40°C (1)	**570**	<10	<10	**250**	10
sample 1 40°C (2)	**330**	<10	**160**	**320**	10
sample 2 40°C (2)	**240**	<10	**320**	**320**	10
sample 3 40°C (2)	<10	<10	<10	**200**	10
blank 1 20°C	<10	<10	<10	<10	10
blank 2 20°C	<10	<10	<10	<10	10
blank 3 20°C	<10	<10	<10	<10	10
sample 1 20°C (2)	<10	**660**	**310**	**60**	10
sample 2 20°C (2)	<10	**360**	**150**	**60**	10
sample 3 20°C (2)	<10	**230**	**210**	**80**	10

Table 1: Volatile Organic Compounds results from various test conditions

Test Conditions	Sample	Mean (µg/cartridge)	Formaldehyde after Blank substraction (µg/cartridge)	LOQ (µg/ Cartridge)	Formaldehyde (µg/day)	PQRI safety threshold (µg/day)
20°C	blank	0.73	1.09	0.10	0.018	0.15
	DPI sample	1.82				
40°C / 75% RH	blank	2.18	0.94	0.10	0.016	0.15
	DPI sample	3.12				

Table 2: Formaldehyde results from various test conditions

Compound	Maximum Quantity Emitted (ug/day)	PQRI SCT (ug/day)
Hexamethyl disiloxane	0.0075	0.15
Methyl-6, 5-hepten-2-one	0.0070	0.15
Nonaldehyde	0.0080	0.15
Dodecane	0.0045	0.15
Styrene	0.0015	0.15
Formaldehyde	0.0180	0.15

Table 3: Volatile organic compounds results in µg/day equivalent

The highest results for each compound in ng/cartridge were converted into µg/day equivalent in Table 3 in order to compare them to the Safety Concern Threshold of 0.15 µg/day reported in the literature.[1] Results were simply divided by 60, considering that a patient will inhale 1 dose per day, i.e. 4 litres per day instead of the 240 litres used here.

DISCUSSION

- Good correlation between compounds detected and extractables from device raw materials, except Methyl-6,5-hepten-2-one and nonaldehyde: Styrene comes from components in ABS, dodecane probably from polypropylene components and hexamethyldisiloxane from the silicone rubber component.
- Higher levels of volatiles generally found at 40°C, which is expected as the higher temperatures tend to increase the release of volatile compounds in polymers. However, this is not the case for methyl-6, 5-hepten-2-one and nonaldehyde. Nonaldehyde seems to be detected only in the presence of a blisterstrip. Methyl-6,5-hepten-2-one may be present due to pollution in the test environment for the series at 20°C. An additional study is in progress to confirm their identification and source.
- Formaldehyde was investigated specifically since some components are made of polyacetal which is known to release formaldehyde (degradation product of polymer).
- When compared to the PQRI SCT, levels of extractables from the Prohaler® DPI are all found to be much lower than the proposed safety concern thresholds.

CONCLUSION

A method to quantify volatile compounds that could potentially be inhaled from a Prohaler® Dry Powder Inhaler was developed and compounds could be effectively recovered and quantified. Several compounds were identified, coming from the various components/materials that constitute the Prohaler® device. However, the levels observed were all much lower than the Safety Concern Threshold of 0.15 µg/day reported by PQRI,[1] which confirms that the materials selected for Prohaler® present no safety risk to the patients.

REFERENCES

[1] PQRI (Product Quality Research Institute), “Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products” (8 September 2006)
[2] M.D. Hodgson, “LC-MS-MS Methodologies for the Quantification of Trace Levels of Extractable/Leachable Components in Dry Powdered Inhaled Formulations”, Drug Delivery to the Lungs vol.19, 212-213, (2008)
[3] USP <601>, Aerosols, Metered Dose Inhalers and Dry Powder Inhalers, USP 32

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