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Kortrijk, July 17, 2019

Report: V2019157
Our Reference: 19150

Project: Analysis of Volatile Organic Compounds in Ointment

Your Reference: Agreement via e-mail
d.d. July 5, 2019
Quotation 00119319 – WP 1

Description of the sample

One jar of ointment

The following information was provided by Dubrovnix:

Cream for psoriasis prevention

Composition: extracts of celandine, calendula, bidens, pepper mint oil, eucalyptus oil, glycerin, perfume of orange, vanilla, mango, and excipients. **Base**: purified solid oil. **Storage conditions**: At +5 to +15 Celcius degree. **Route of administration**: apply gently rubbing in disease sites. **Date of manufacture**: March 15, 2018. **Shelf life**: 36 months. DSTU 4765:2007.

Analytical Method

Volatile organic compounds (VOCs), including residual solvents, benzene, toluene and xylenes, were analysed by static headspace (SHS) in combination with gas chromatography – mass spectrometry (GC-MS).

An aliquot of the sample is placed in a closed vial. The sample was thermostated at 80°C and 1 mL of the headspace gas was injected in the GC-MS system. Separation was done on a thick film apolar column. Mass spectrometric detection was done in scan mode.

Results

The total ion chromatogram (TIC) in full scale obtained for the ointment sample is given in Figure 1. The first two peaks correspond to air and water and can be discarded. An enlarged total ion chromatogram is shown in Figure 2. In this chromatogram, 9 volatile organic compounds can be detected. The identity of these compounds, together with retention times and concentrations are listed in Table 1. The concentrations were determined using standard addition. For comparison, the limit values according to ICH guidelines (https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-14.pdf) are also included. The levels of the detected VOCs are well below the ICH guideline values.

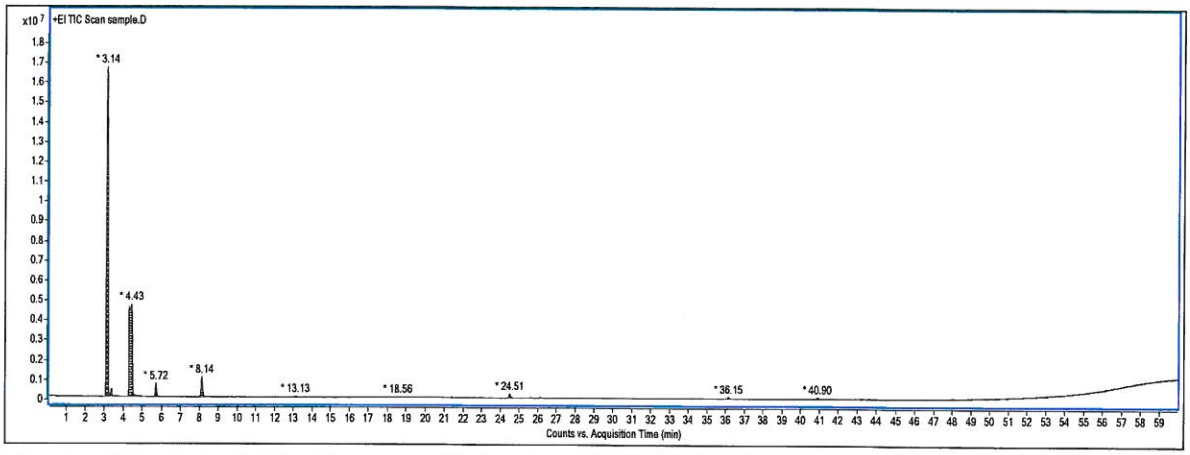

Fig. 1: Total ion chromatogram obtained by SHS-GC-MS for ointment.

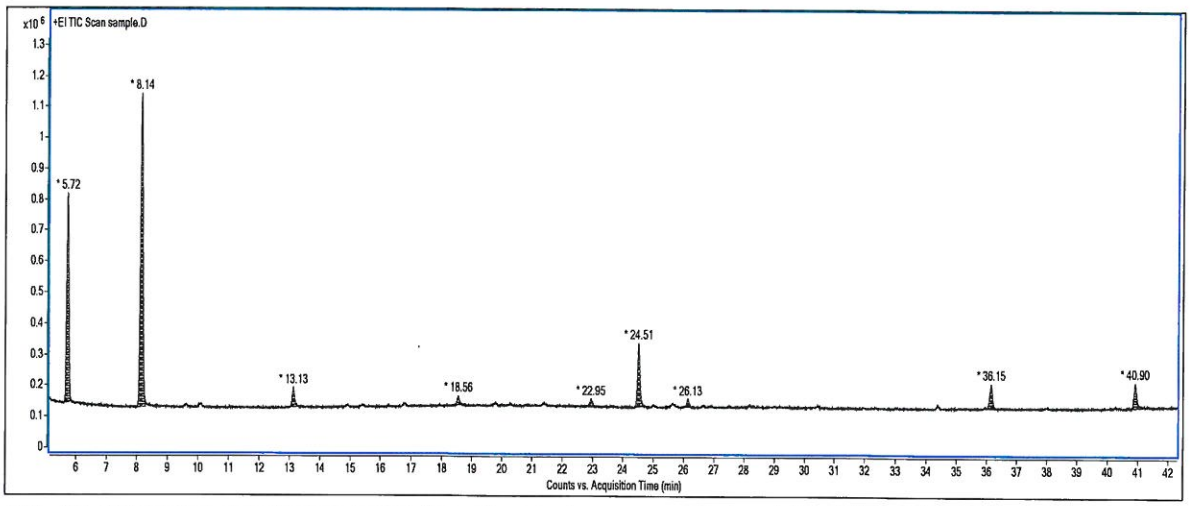

Fig. 2: Enlarged (zoomed) total ion chromatogram obtained by SHS-GC-MS for ointment.

Table 1: Detected VOCs in ointment sample

Peak	RT (min)	Identification	Concentration (ppm)	ICH (ppm)
1	5.72	methanol	28	3000
2	8.14	ethanol	31	5000
3	13.13	1-propanol	2.3	5000
4	18.56	1-butanol	1.0	5000
5	22.95	methylcyclohexane	1.5**	1180
6	24.51	toluene	17	890
7	26.13	octane	1.3**	5000*
8	23.15	eucalyptol	***	
9	40.90	menthol	***	

*= value for n-heptane
**= this concentration is calculated versus n-heptane. The TIC response was used.
***= present in formulation

In addition, special attention was given to the presence volatile aromatic hydrocarbons such as benzene, toluene, ethylbenzene, xylenes and naphthalene. Using extracted ion chromatograms (EICs), the obtained datafiles were analysed. The extracted ion trace (ion m/z 78) for benzene is shown in Figure 3. A minor trace of benzene is detected at 19.25 min. The EIC for toluene, ethylbenzene and xylenes (m/z 91) is shown in Figure 4. Toluene is clearly detected at 24.51 min and traces of ethylbenzene (28.85 min), m/p. xylene (29.17 min) and o.xylene (30.28 min) are also present. As illustrated by the "blank" EIC at m/z 128 in Figure 5, no naphthalene is detected. The concentrations of these volatile aromatic hydrocarbons were determined using an external standard. The obtained concentrations are given in Table 2. All levels are well below the ICH guideline levels.

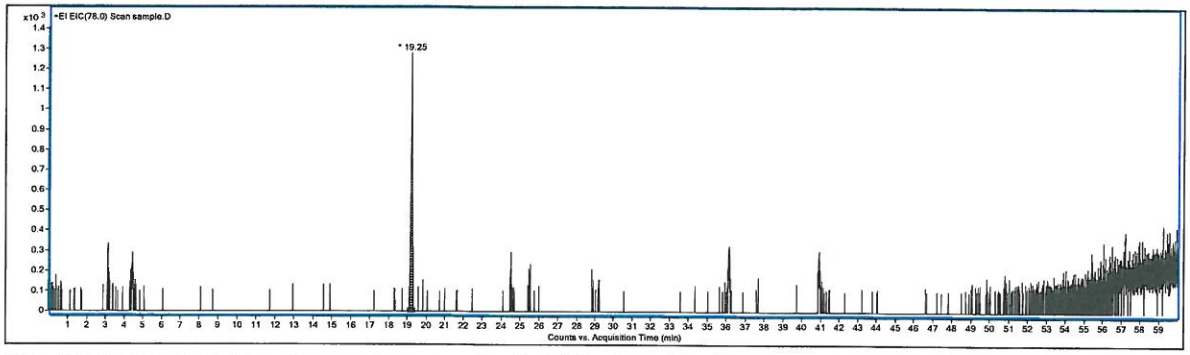

Fig. 3: Extracted ion chromatogram (m/z 78) showing the presence of a trace of benzene.

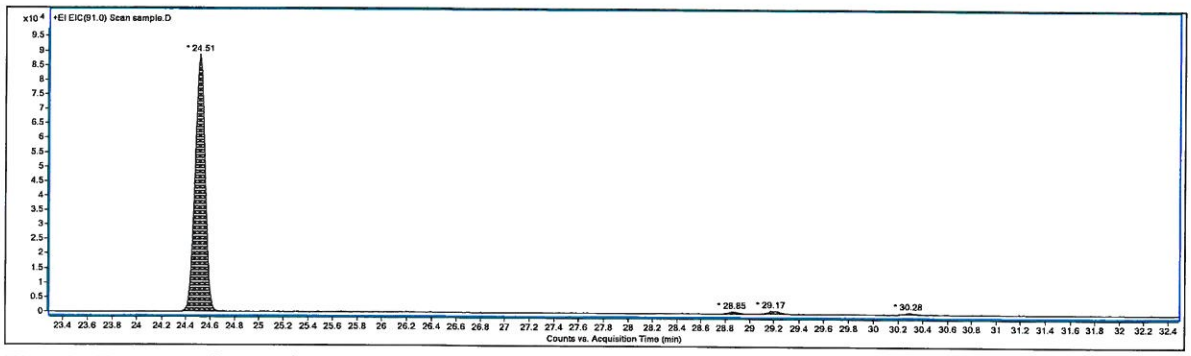

Fig. 4: Extracted ion chromatogram (m/z 91) showing the presence of toluene (24.51 min) and traces of ethylbenzene (28.85 min), m/p-xylene (29.17 min) and o-xylene (30.28min).

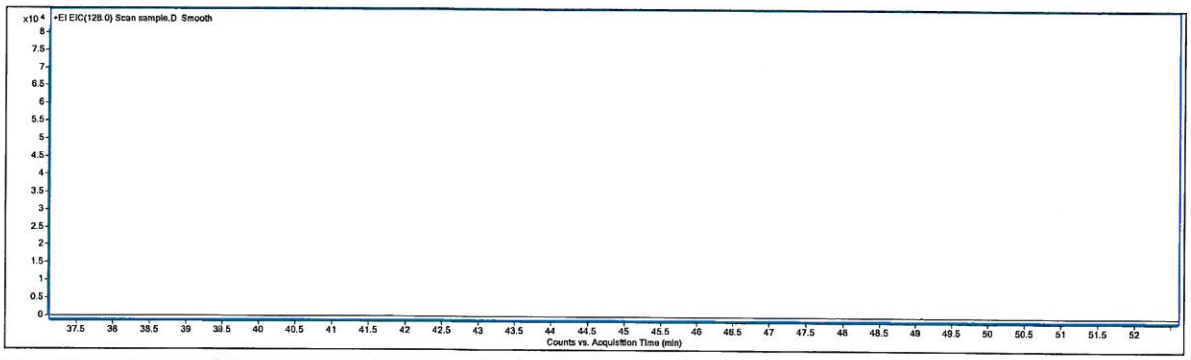

Fig. 5: Extracted ion chromatogram (m/z 128) showing the absence of naphthalene.

Table 2: Detected volatile aromatics in ointment sample

RT (min)	Identification	Concentration (ppm)	ICH (ppm)
19.25	Benzene	0.11	2
24.51	Toluene	17	890
28.85	Ethylbenzene	0.26	
29.17	m/p-xylene	0.64	
30.28	o-xylene	0.28	
	Sum xylene	0.92	2170
41.78	naphthalene	<0.1	

Conclusions

1. Traces of residual solvents were detected. Identified volatile organic compounds were: methanol, ethanol, 1-propanol, 1-butanol, methylcyclohexane, toluene, and octane. The concentrations of these compounds were below the ICH guideline levels.

2. A trace of benzene was detected (0.1 ppm), well below the ICH guideline level (2 ppm).

3. Traces of xylenes were detected. The sum of the concentrations of the xylene isomers was well below the ICH guideline level.

4. No naphthalene was detected (< 0.1 ppm).

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