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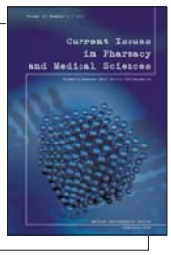

Application of sHS/GC-MS method for the identification of paracetamol impurities in the selected pharmaceutical formulations

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ABSTRACT

Simple and rapid quantitative procedure based on gas chromatography mass spectrometry in combination with static headspace was developed for the identification of paracetamol and its impurities in commercially available analgesic tablets. The proposed procedure provides relevant analytical results and an uncomplicated sample procedure. Samples were separated on HP5-ms capillary column using helium (1.5 ml min^{-1}) as carrier gas. The qualitative identification of analysed compounds was carried out on a triple quadrupole mass spectrometer in scan mode equipped with electron impact ionisation (EI) and recognised by NIST Library (NIST Library match 90%). The elaborated procedure is suitable for the identification of paracetamol, its impurities (*N*-phenylacetamide. *N*-(2-hydroxyphenyl)acetamide) and volatile organic compounds.

Keywords: paracetamol. impurities. headspace analysis. GC-MS

INTRODUCTION

There is a growing requirement for the quick, cheap and simple methods to obtain the research results for use by pharmaceutical industry. The impurities profile has become essential as an important requirement for active pharmaceutical ingredients and excipients. It may be used for specific quality control (QC), and due to utility, for fingerprinting applied to identify and confirm producer.

Paracetamol is an analgesic and antipyretic drug available in several pharmaceutical formulations commonly recommended to large variety of patients. The European Pharmacopoeia monograph on paracetamol specifies several impurities including *N*-(2-hydroxyphenyl)acetamide, *N*-phenylacetamide, or 4-aminophenol. Those impurities may originate from synthesis or degradation of paracetamol and they may increase the risk of harm at mass consumption.

A literature survey reveals the reports concerning analysis of organic impurities [2] of paracetamol such as high performance liquid chromatography [5] and thin-layer chromatography [4]. To the best of our knowledge there are no static headspace gas chromatography mass spectrometry (sHS\GC-MS) methods, enabling identification of paracetamol organic impurities in its formulations.

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The most useful and recommended method for identification and quantification of volatile compounds presented in pharmaceuticals, due to its extremely separation efficiency and unique feature of the standardised identification of the analysed compounds, is capillary gas chromatography [6]. Headspace technique [1] is routinely used for the organic volatile impurities (OVI) analysis and chemical signatures of pharmaceuticals especially at combination with solid-phase micro extraction [3].

In the presented work, the chemical profile of the selected paracetamol tablets and its potency as a simple and rapid tool for identification of the presence of impurities and QC of pharmaceuticals has been reported.

MATERIALS AND METHODS

Chemicals: Acetaminophen standards was purchased from Sigma (St. Louis, MO, USA). Pharmaceutical formulations (analgesic tablets) were purchased from local market (denoted as preparation A and B).

GC conditions: sHS\GC-MS analysis was performed using 7890A Agilent GC system coupled with 7000 Agilent triple quad mass spectrometer operated in electron impact ionisation (70eV) and combined with 7697A Agilent headspace sampler (Palo Alto, CA, USA). The temperature of front inlet, transfer line, ion source, and quadrupole was set at 250, 230, 280, and 150°C, respec-

tively. Separation was carried out using HP5-ms ((5% phenyl)-methylpolysiloxane), 30 m x 0.25 mm i.d., 0.25 µm film thickness) with helium of high purity (99.9999%, Messer, Chorzów, Poland) as carrier gas at a constant flow of 1.5 ml min^{-1}. The initial oven temperature was 30°C (held 2 min) and increased to 250°C (held 5 min) at rate of 10°C min^{-1}. The headspace (HS) sampler was connected to the GC front inlet via a heated fused silica capillary transfer line through the split\splitless injector operated in pulsed splitless mode (pulse pressure 50 psi until 0.1 min). A 1 ml sample loop was employed. The temperature of HS oven, loop and transfer line was set at 150, 170, and 180°C, respectively. The mass detector was operated in scan mode and the data was carried out over a mass range of m/z from 30 to 450 at a rate of 4 scans s^{-1}. The analytes were positively identified by comparison of their mass spectra with those collected in the NIST (National Institute of Standards and Technology) Library (mass spectra library v. 2.0 f, build Oct. 22 2009). The system was operated by Agilent MassHunter B.05 software.

The extraction of impurities from the examined tablets was performed using 20 ml HS vials containing 1.0 g of powdered tablet. The vials were sealed with a PTFE-lined septum and an aluminium crimp cap, and then conditioned for 30 min at 150°C. Once equilibrium was reached the vials were pressurised to 14 psi within 1 min (flow to pressure). The sample was injected to the GC with a sampling time of 0.5 min.

RESULTS

sHS\GC-MS method was applied to identification of paracetamol organic impurities potentially presented in investigated tablets. The proposed procedure allows the identification of 17 different compounds. Most of the components identified in all of the analysed samples were characterised by insufficient matching (<90%) to NIST Mass Spectra Library. Several volatile compounds and parace- tamol organic impurities such as *N*-(2-hydroxyphenyl)acetamide, *N*-phenylacetamide, and 1-(4-hydroxyphenyl)etanone were detected. The identified organic impurities (match 90%) of analysed tables are presented in table 1. An exemplary volatile profile obtained for the standard and selected paracetamol tablets are shown in figure 1.

Table 1. The selected compounds (NIST database matching 90%) identified in the investigated paracetamol tablets

Compound	RT [min]	Match [%]	PTA [%]
1-methanone	11.060	91.00	0.01
Acetic acid	3.370	91.10	0.11
Menthol (3)	11.421	98.07	9.78
N-(2-hydroxyphenyl)acetamide (2)	17.978	96.25	5.61
N-phenylacetamide (1)	14.974	93.21	1.39
Phenol (4)	7.831	94.83	9.01

PTA – percent of total area of the chromatogram; RT – retention time; 1-4 the impurities

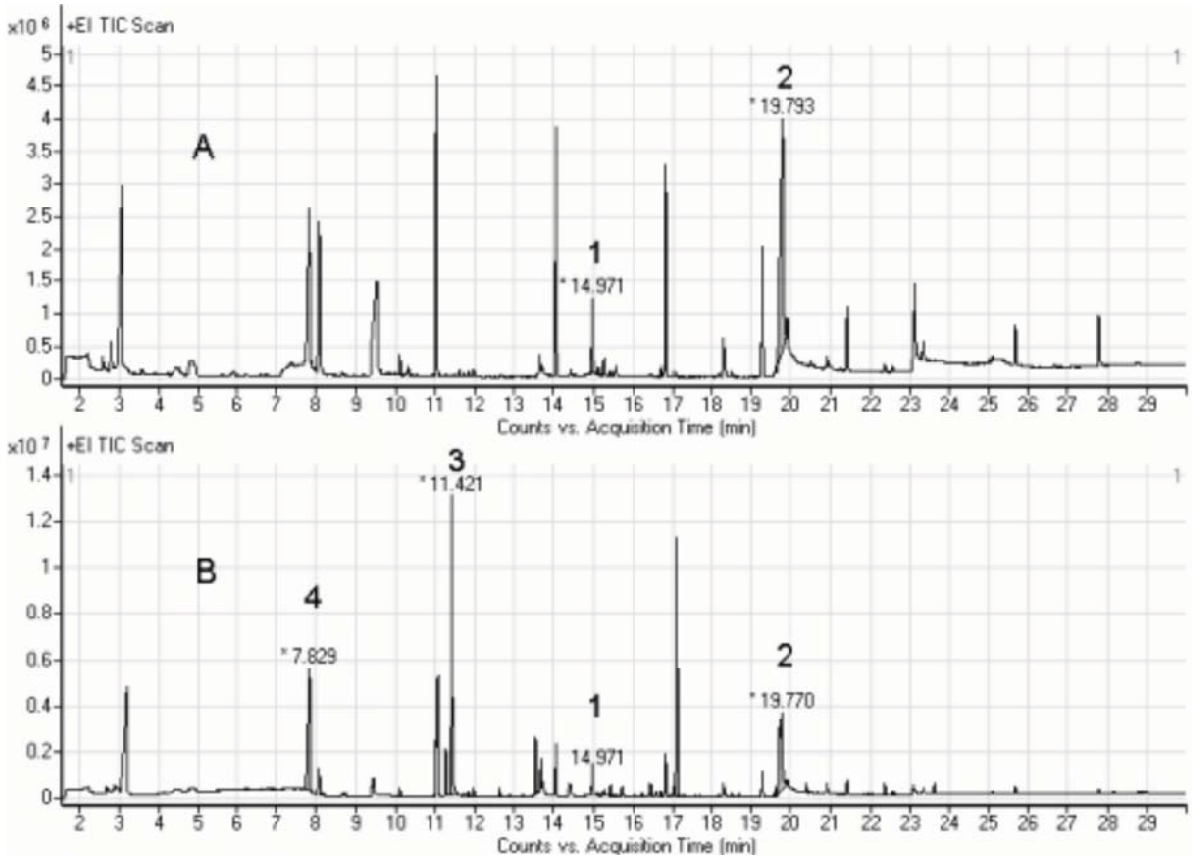

Fig. 1. sHS\GC-MS full scan total ion chromatogram of volatile profile obtained for the investigated tablets (1-4, the identified impurities)

CONCLUSIONS

The described static headspace gas chromatography mass spectrometry (sHS\GC-MS) method has been successfully applied for the identification of the paracetamol impurities (Ph.Eu. 7.0) and volatile organic compounds (VOC's) screening. The elaborated method offers an interesting alternative for QC falsification control and identification of the unknown identity pharmaceuticals. In addition, proposed procedure, automated and uncomplicated, requires no solvents and inconsiderable preparation of the sample.

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