Postprint of: Aszyk J., Woźniak M. K., Kubica P., Kot-Wasik A., Wasik A., Concentration levels of selected analytes in the gas phase of an e-cigarette aerosol, MICROCHEMICAL JOURNAL, Vol. 148 (2019), pp. 717-724, DOI: 10.1016/j.microc.2019.05.052

Concentration levels of selected analytes in the gas phase of an e-cigarette aerosol

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In Memoriam

We would like to honor the memory of Prof. Jacek Namieśnik, who has sadly passed away. We salute You for Your tenacity of purpose and outstanding leadership qualities. Thank You for words of encouragement and support. We will remain forever grateful.

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Abstract

The aerosols generated from e-cigarettes are composed of liquid and gas phases resulting from vapourized e-liquid. The apportioning of substances from e-liquid into the liquid and gas phases during e-cigarette use has not been extensively studied. Partitioning of e-liquid components between the gas and the liquid phase of the aerosol influences the substances inhaled and exhaled by the users, leading to second-hand exposure. It seems important to determine which compounds and how much of them are transferred into the gas phase and may immediately enter the bloodstream. For this purpose, a method based on thermal desorption followed by gas chromatography coupled with tandem mass spectrometry (GC–MS/MS) in electron ionization mode was developed. As in a previous study, an automatic generator of an aerosol from an e-cigarette with a collection tube filled with *melt-blown* non-woven fabric discs and equipped with Tenax TA sorption tubes was used. The *melt-blown* non-woven fabric is designed to capture liquid phase compounds, while sorption tubes are meant to sorb compounds in the gas phase of the aerosol. To control the e-liquid mass changes before and after a puff session, quantitation based on the mass change tracking approach (MCT) was applied. Accuracy of the developed method ranged between 91% and 110% regardless of the spiking level, with precision and reproducibility better than 10%. The limits of detection (LODs) ranged from 0.015 to 0.076 ng of substance emitted/mg of consumed e-liquid, while limits of quantitation (LOQs) ranged from 0.045 to 0.23 ng of substance emitted/mg of consumed e-liquid. Most of the compounds are deposited in the liquid phase of the aerosol, while only trace levels of some substances may be observed in an actual, non-condensed gas phase.

Keywords

electronic cigarettes; gas chromatography–tandem mass spectrometry; smoking machine; e-cigarette aerosol collection; flavouring compounds; nicotine;

1.Introduction

An e-cigarette provides nicotine to the user through an aerosol generated by heating a liquid containing this alkaloid. The aerosol that is formed primarily contains base components of e-liquid (propylene glycol, glycerol), nicotine and flavouring additives [1]. The use of such a device is believed to simulate an experience similar to smoking traditional cigarettes. There is mixed scientific evidence as to whether or not e-cigarettes play a role in cigarette smoking cessation.According to some scientific research, e-cigarettes do not affect the process of giving up smoking and are perceived by some as a similar threat or are used interchangeably with traditional cigarettes [2–4]. However, other research shows that people who use e-cigarettes treat them as an alternative to traditional cigarettes and consider them less harmful [2,5,6]. However, some users often find that e-cigarette use helps in quitting traditional tobacco smoking [7,8].

In the properly functioning heating element of the e-cigarette, there should be no combustion process. The user activates the power supply of the heaters in the atomizer, which results in the heating up of the liquid to a sufficiently high temperature, and thus the formation of an aerosol occurs during rapidly cooling in stream of passing air [9]. The aerosol is inhaled, and the nicotine contained in it and other compounds are absorbed through the mucus, upper respiratory tract, and the alveoli of the lung [10].

The aerosols generated from e-cigarettes that come into direct contact with the respiratory system are composed of liquid and gas phases resulting from vapourized e-liquid. The aerosols generated from the e-liquids are still of interest to many scientists. Currently, there is no standardized puffing regimes for e-cigarette aerosol measurements. In 2015,CORESTA E-Vapour Sub-Group, formed in 2013 has published Recommended Method (CRM) No. 81 for aerosol generation and collection, suggesting 55 mL volume, 3 s puff duration and 30 s puff interval as standard conditions for aerosol generation [11]. However, in CORESTA Technical Guide No. 22, for the Selection of Appropriate Intense Vaping Regimes for E-Vapour Devices, available from February 2018, the selection of topography data may be performed regarding to literature topographical data, specified in guide and considering the parameters affecting aerosol delivery [12].

To date, several methods of different efficiency have been developed to capture e-cigarette aerosols. The simplest way is to connect the e-cigarette with a syringe, which results in complete aerosol capture [13]. Other popular methods utilize single wash bottles or wash bottles connected in series, filled with appropriate solvent and/or derivatizing agent, to trap the aerosol formed during e-cigarette use [14–18]. Some researchers use e-cigarettes

connected directly to thermal desorption (TD) tubes [19,20]. A high efficiency of trapping the aerosol liquid phase can be achieved by sampling methods that utilize Cambridge filter pads (CFP) [17,21–23]. The most sophisticated devices are programmable units capable of automatic aerosol generation and trapping using different sorbents [24–27].

The partitioning of analytes between liquid and gas phase of e-cigarette's aerosol has not been extensively studied [28]. Up to the Authors knowledge, only one method utilizing automatic device for the collection of the complete aerosol (liquid and gas phase) during the same session of smoking was presented. In this study 44-mm inline CFP followed by glass impinger filled with DNPH was used for collection of carbonyl compounds in liquid and gas phase analysis respectively [18]. In addition, there is a need to study the gas phase, which has a relatively small overall contribution but the potential to immediately enter the bloodstream.

For this purpose, a previously described machine was used [27], and the assumption was that the *melt-blown* fabric used did not retain the gas phase as described by Jackiewicz et al. [29]. The hypothesis is that part of the aerosol can be deposited in the gas phase and not adsorbed onto *melt-blown* fabric, which results in the possible transfer of trace amounts of analytes from e-liquid to the gas phase of the aerosol.

The modular structure of the constructed device and the ease of its modification enabled the installation of a TD tube downstream of the stainless-steel tube packed with *melt-blown* fabric onto which the liquid phase of the aerosol has been adsorbed, thus making it possible to capture both the gas and the liquid phase of the aerosol and analyse them for the content of the same flavouring compounds (including nicotine) that are found in the e-liquids [30–32]. It seems important to study which compounds and how much of these compounds are transferred into the gas phase, assuming that the total liquid phase generated has been adsorbed. The samples of the model e-liquid and the liquid phase of aerosol generated from them together with real samples were analysed in a manner similar to the manner of analysis described in the previous research [27]. To check whether aerosol recovery was reproducible, MCT (mass change tracking) approach was used [15,33]. The TD-GC-MS/MS was used in the final determination, which allowed qualitative and quantitative analysis of adsorbed compounds.

2. Materials and methods

2.1. Reagents and standards

Thirty four standards used in a previously published study [27] were obtained from Sigma-Aldrich (St. Louis, USA): 2-acetylpyridine, 2-acetylpyrrole, 2-isopropyl-4-methylthiazole, 2,3,5-trimethyl-pyrazine, 2,3,5,6-tetramethylpyrazine, 4-methylacetophenone, benzaldehyde, benzyl acetate, benzyl alcohol, ethyl vanillin, ethyl 3-(methylthio)propionate, ethyl maltol, eugenol, furaneol, furfural, isoamyl isovalerate, isopentyl acetate, leaf aldehyde, leaf alcohol (*cis*-3-hexen-1-ol), L-menthyl acetate, maltol, melonal, menthol, menthone, methyl cyclopentenolone, *n*-hexanol, nicotine, theaspirane, *trans*-2-hexenol, vanillin, β-damascone, γ-nonanolactone, γ-undecalactone, γ-decalactone. Naphthalene-d_8 was used as the internal standard (IS) and was purchased from Isotec/Sigma-Aldrich (St. Louis, USA). Vegetable glycerine (VG) and propylene glycol (PG) were purchased from Anwit (Warsaw, Poland). Methanol (MeOH, MS grade) was obtained from Merck (Darmstadt, Germany). *Melt-blown* non-woven sheets were donated by EkoKomes (Kolnik, Poland). TD sorption tubes Tenax TA (1/4″ × 3.5″, TD stainless steel tube, Tenax TA 35/60 mesh) were purchased from Supelco/Merck (Darmstadt, Germany).

2.2. Real samples

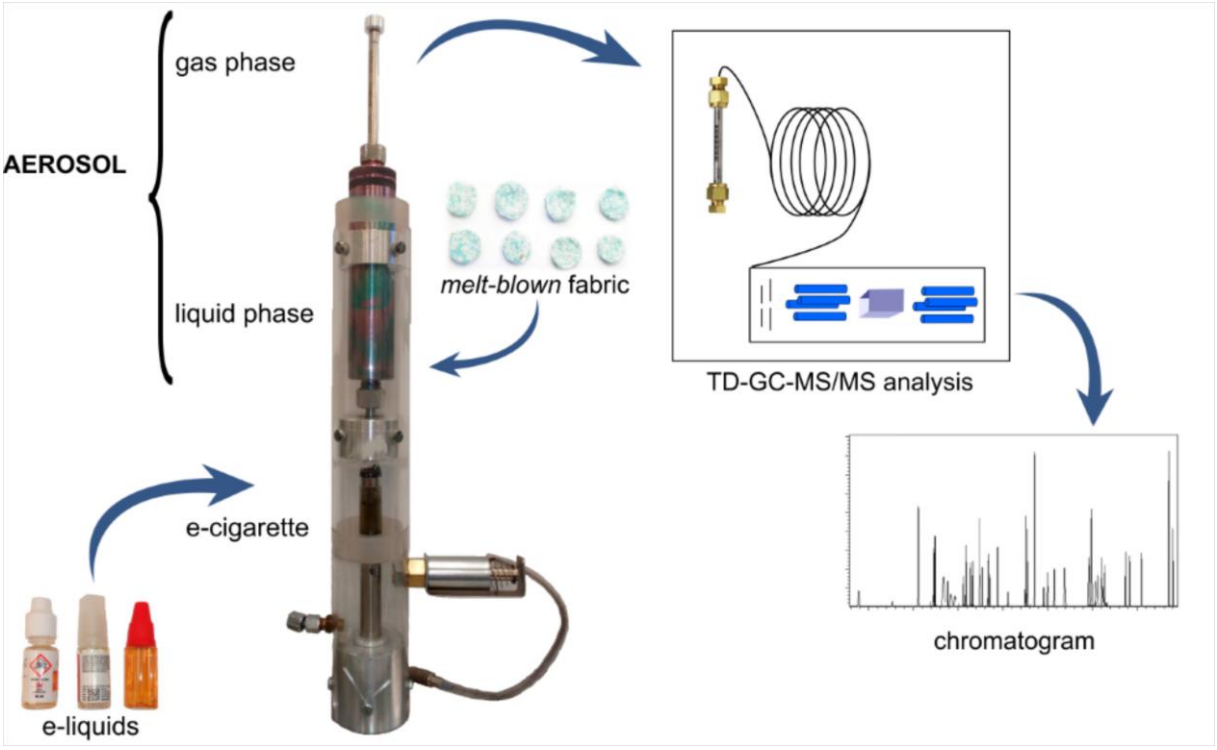
For verification of applicability of proposed method eight e-liquids samples was selected. These e-liquid samples were previously examined for evaluation of concentration of tested analytes in liquid phase of an e-cigarette aerosol [27]. E-liquids were bought on the local market (shops in Gdańsk, Poland) from four companies. The concentration of nicotine in selected e-liquids was in the ranges of 6 to 18 mg/mL in tobacco, strawberry, vanilla, menthol, cherry, black tea and apple flavour. The selection of flavour was performed based on questionnaires carried out among sellers regarding their popularity. Samples were analysed within two weeks of purchase. Each sample was stored at room temperature without sunlight, similar to the shop conditions.

2.3. Gas phase e-cigarette aerosol sampling process

For sampling of gas phase of e-cigarette aerosol, TD tubes filled with Tenax TA were applied. In the preliminary studies Tenax® TA sorbent was chosen since it can efficiently trap

wide range of flavouring compounds (C6–C30), while not retaining methanol, which was used as a solvent.

TD tubes were installed downstream of the liquid phase collection tube filled with 5 *melt-blown* discs. *Melt-blown* non-woven fabric was applied to collect the liquid phase and to ensure the sorption of only the gas phase on TD tubes. The same puffing conditions and the same sampling protocol as in the previous study were applied [27]. In brief, the puffing protocol included 10 puffs, 1 puff every 15 s, 4 s puff duration, 50-mL puff volume and 750 mL/min flow rate. The e-cigarette battery was fully charged before conducting each puff set. Before each repetition, the tank of the e-cigarette was filled to the same level, and the session was repeated. To ensure repeatability and to eliminate the influence of the temperature on aerosol generation, a 30-min resting period was applied before conducting each repetition. Additionally, the mouthpiece was properly cleaned to remove any possible condensed aerosol on it during each puff session. One coil was assigned for one type of e-liquid analysed. The MCT approach was applied to evaluate the mass of e-liquid consumed during each puffing session and the mass gained on the sorbent: the EC device and collection tube filled with *melt-blown* non-woven fabric were weighed before and after each repetition. After aerosol generation, the TD tube was demounted from the sampling apparatus, capped and transferred for TD analysis. The general procedure of aerosol generation and trapping is presented in the Fig. 1.



2.4. Blanks

An air blank on the TD tube without an e-cigarette installed in the automatic aerosol generator was collected using 10 puffs (500 mL of air) of laboratory air. Notably, indoor air was passed through activated carbon filters mounted in the device. Additionally, all elements of the e-cigarette aerosol generator were carefully washed with isopropyl alcohol before conducting each puff session to avoid cross-contamination and any carryover effect. Second, between each of the puffing sessions, a TD tube with 10 puffs collected from vapourized analyte-free e-liquid prepared from PG (65%), VG (30%), and H_2O (5%) produced with an e-cigarette was analysed. Control blanks were performed between each puff session to ensure proper analytical performance. As a result, only benzaldehyde was detected in blank samples, possibly as a result of degradation of the Tenax TA sorbent during the desorption step. Therefore, all benzaldehyde concentrations herein reported were corrected according to its presence in the blank samples. Nonetheless, no other compounds were detected in the blank samples that were collected.

2.5. Standards, calibration solutions and validation formulations

Seven- or eight-point calibration curves were made with each level prepared in triplicate (n=3). Calibration solutions were prepared in MeOH to obtain the desired measuring range specific to each compound (in general 10-2500 ng). For each TD tube, the IS amount was kept at the same level (100ng).

For the preparation of calibration standards, 2 µL of standards was injected on the inlet side of the TD tube. The prepared TD tube was mounted on top of the generator collection tube, and 10 puffs of analyte-free e-liquid (65% PG: 35% VG: 5% H_2O, w/w/w) were collected. The resulting gas phase was passed through the previously loaded TD tube. After demounting of the TD tube and before each analysis, the carrier gas was passed through the TD tube with a flow rate of 20 mL/min for 1 min to remove excess solvent. Calibration curves were constructed using the peak area ratio (analytes vs IS) plotted against the corresponding concentration. For method validation, sorption tubes were spiked at two levels (100 ng and 1000 ng) and were subsequently loaded by blank 10 puffs of analyte free e-liquid. Validation samples were used for evaluation of the accuracy and precision of the procedure that had been developed.

To verify the analyte concentration in the gas phase, a model e-liquid was prepared by dissolving standards in analyte-free e-liquid (65% PG: 35% VG: 5% H_2O, w/w/w) to obtain concentrations of each substance of approximately 1 mg/mL, as previously described [27].

2.6. GC-MS/MS parameters

The analysis was carried using a thermal desorber (TD-30R Thermal Desorption System, Shimadzu, Kyoto, Japan) coupled with a gas chromatograph (GC-2010 PLUS System, Shimadzu, Kyoto, Japan) and tandem mass spectrometer (TQ8050, Shimadzu, Kyoto, Japan). For the separation of the target compounds, a capillary ZB-WAX (30m x 0.25 mm i.d., 0.25 µm film thickness was applied (Phenomenex, USA). The oven temperature programme was set as follows: 50°C for 4 min, 10°C/min to 150°C, hold for 3 min, then 20°C/min to 250°C and a hold for 3 min. The injection split ratio was set to 1:50. The MS parameters were set as follows: temperature of the transfer line: 285°C and ion source temperature: 220°C. Helium was applied as a carrier gas (purity ≥ 99.999%) at an initial flow rate of 1 mL/min, and then the linear velocity was controlled at 36.6cm/s by the system. Argon (purity ≥ 99.999%) was applied as the collision-induced dissociation (CID) gas. Thermal desorption of tubes was carried out at 280°C with a helium flow rate of 60mL/min for 10min. The cold trap was maintained at -10°C. After primary desorption, the cold trap was heated from -10°C to 250°C (secondary desorption) and kept at this temperature for 2 min. The temperature of the joint, valve and transfer line was set at 250°C. A pre-purge step (1 min) with carrier gas flow at 20 mL/min was applied to remove solvent (methanol) from the sorption bed. The specific multiple reaction monitoring (MRM) conditions were set as in a previous study [31]. Two MRM transitions (quantifier and qualifier) were monitored. For verification of the presence of the target compounds in each sample, the quantifier/qualifier transitions ratios were monitored. Data acquisition and quantitation were accomplished using GCMS Solution (version 4.45, Shimadzu Corporation) and TD-30 Control Software.

3. Results and discussion

3.1. Method evaluation

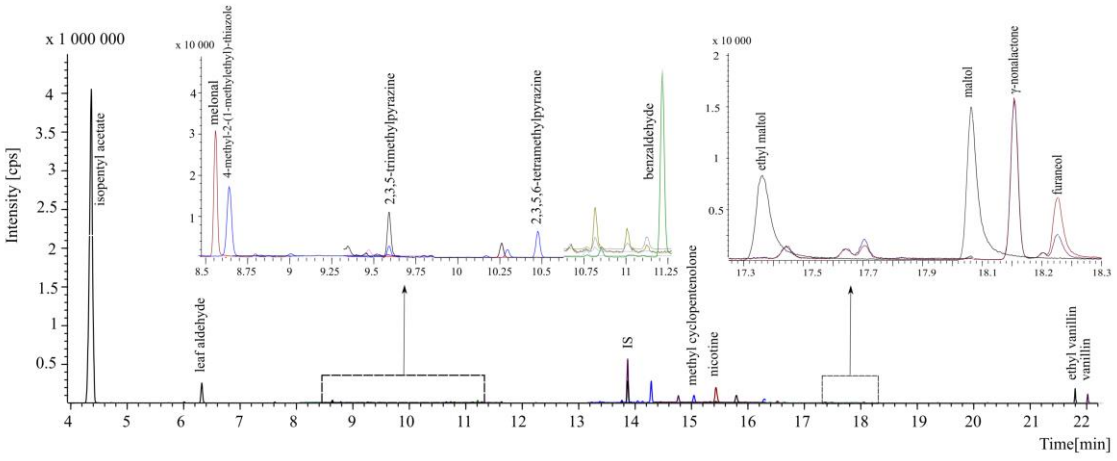
3.1.1. Breakthrough assessment

Due to the high collection flow rate (750 mL/min) during aerosol generation, possible breakthroughs needed to be evaluated and were verified by collection of 10 puffs of model e-liquid on two TD tubes connected in series during sampling. The analysis of the second tube showed negligible breakthrough (<5%) for all of analytes detected in the gas phase in comparison to the first tube. Breakthroughs at levels below 5% can be neglected [34].

Moreover, additional experiments were performed to verify if a high flow rate may lead to a loss of analytes that were already adsorbed. For this purpose, two set of experiments were performed. Briefly, 2 µL of standard mixture of 50µg/mL in MeOH was injected onto TD tubes, separately before and after collection of 10 puffs of vapourized analyte-free e-liquid. No significant difference was observed, both in retention times and peak response of analytes, between two sets of experiments, which confirmed that a high flow rate had a negligible impact on analyte adsorption.

3.1.2. Model e-liquid testing

To study the release of the compounds from e-liquid to the gas phase, model e-liquid with target analytes at a concentration of 1 mg/mL was tested. Six repetitions (6 puffing sessions, each of 10 puffs) with the use of the same coil and with conditions described in Section 2.2. were performed. To ensure analytical performance, MCT was applied. Uptake of the liquid phase of the aerosol was preventively checked and was maintained at the same level as previously reported [27] and was equal to 92.0 ± 1.3%. Example of the chromatogram obtained during the analysis of the gas phase of the model e-liquid is presented on Fig.2. **Table 1** shows a summary of the levels of target analytes collected on the TD tubes.



The concentration of analytes in the gas phase was expressed in both ng/mg of consumed e-liquid and in ng/10 puffs to facilitate comparison with emissions levels of target analytes in the aerosol liquid phase. The average amount of e-liquid aerolized was 123.4 ± 5.1 mg (n=6). Fifteen of the thirty-four compounds were detected in the gas phase generated from the model e-liquid.

Additionally, device variability was evaluated. Three tanks each equipped with new coils were vaped with model e-liquid by an automatic aerosol generator. The average amount

of e-liquid aerolized was 128.3 ± 1.5 mg (n=3). The concentrations (expressed in ng per mg of consumed model e-liquid) were as follows: nicotine: 1.11 ± 0.83; isopentyl acetate:44.9 ± 4.0; leaf aldehyde: 8.9 ± 1.8; melonal: 0.143 ± 0.097; 4-methyl-2-(1-methylethyl)-thiazole: <LOQ; 2,3,5-trimethylpyrazine: <LOD-(0.054)*; 2,3,5,6-tetramethylpyrazine: <LOD-<LOQ; benzaldehyde: <LOQ; methylcyclopentenolone: <LOD-<LOQ; maltol: <LOD-(0.106)*; ethyl maltol: <LOD-(0.158)*; γ-nonalactone: <LOD-<LOQ; furaneol: <LOQ-(0.156)*; ethyl vanillin: <LOQ-(0.45)*; vanillin: <LOQ-(0.71)*. The concentration marked ()* means that only one result was above LOQ, and therefore, SD was not given. The within- and between-device repeatability revealed the same level of the compounds released during the 10-puff sessions.

The aerosol generated from e-cigarettes, in physicochemical terms, is a colloidal system, in which the liquid phase is dispersed in a gaseous phase. Given that volatile, semivolatile and non-volatile substances are present in the e-liquid, these substances can be released into the gas phase as a result of heating or can be adsorbed on the particles of the dispersed liquid phase, depending on the partition coefficient of the analyte between the two phases. However, the presence of these compounds in both phases is often neglected, which consequently can cause confusion when discussing issues such as liquid-gas partitioning of e-cigarette aerosols. The gas phase of the e-cigarette aerosols is composed primarily of ambient atmospheric species, i.e., oxygen and nitrogen, drawn in and through the e-cigarette during puffing [35]. Based on a previous study [27], most of the compound is deposited mainly in the liquid phase of the aerosol, while only trace levels of some substances may be observed in an actual, non-condensed gas phase. The data provided demonstrate significant variability in the release of substances between puffing sessions. Notably, the release of very volatile compounds into the gas phase (for example, isopentyl acetate and leaf aldehyde) was repeatable, while emission concentrations of less volatile compounds, such as nicotine, ethyl vanillin and vanillin, appeared to vary. Many factors could have an impact on these results. First, the chemical equilibrium between the liquid and gas phase of e-cigarette aerosol is not easily maintained. Although each puffing session was performed in the same manner, clearly the rate of absorption of e-liquid into the atomizer coil and its temperature when activated is not controlled and kept at the same level. The dynamic character of the aerosol generation process may explain the range of emission concentrations observed for compounds released into the gas phase, especially in the case of lower levels of concentration. Second, the distribution of the substances across gas and liquid phase depends on their vapour pressure. The analyte with a high vapour pressure will be more volatile and will transfer to the gas

phase. However, the presence of PG and VG, acting as humectants, may affect the partition coefficient of compounds, especially the polarity between the gas and liquid phase. The affinity of PG/VG for polar compounds will retain a portion of ingredients in the liquid phase as a result of hydrogen and van der Waals forces [28]. Moreover, water present in the aerosol may influence gas phase partitioning of semivolatile compounds. Additionally, compounds such as vanillin and ethyl vanillin, because they have three reactive functional groups (aldehyde, phenol hydroxyl and aromatic), may undergo different types of reactions with PG, leading to formation of vanillin and ethyl vanillin propylene glycol acetals, which may affect their repeatable release into the gas phase [36].

3.2. Method validation

The method outlined in the present study was validated according to the guidelines for analytical method validation [37–39]. To determine the values of analyte recovery from the TD tube, a second run on the same tube was performed. No peaks of analytes were observed in the chromatogram of the second run.

The GC-MS/MS matrix effect (ME%) was evaluated at two concentration levels (100 ng and 1000 ng). The ME (%) was evaluated by comparing the responses of standards in MeOH spiked onto TD tubes with those obtained for standards spiked onto TD tubes, which were subsequently loaded with 10 puffs of analyte-free prepared e-liquid. The ME was calculated according to the following formula: ME (%) = $(\frac{A/A_{IS(m)}}{A/A_{IS(s)}} - 1) * 100\%$, where $A/A_{IS(m)}$is the response of the analyte in the matrix and $A/A_{IS(s)}$ is the response of the analyte in the solvent. Most of the compounds had negligible matrix effects (-20%≤ME≤20%). Nonetheless, three compounds exhibited significant ion enhancement for the low concentration level: maltol, ethyl maltol and furaneol (55%, 52% and 31%, respectively). In view of the above, matrix-matched calibration curves were employed for quantitation and validation purposes.

The linearity of the calibration curves was assessed within a concentration range specific for each compound at seven or eight concentration levels (*n*=3). The coefficients of determination were higher than 0.9980. Parameters of the calibration curves are summarized in **Table 2**.

The limits of detection (LODs)and limits of quantitation (LOQs) were calculated from the regression parameters [30–32]. The LOD values were in the range from 1.9 to 9.6 ng on tube, while LOQ values were in the range of 5.7-29 ng on tube. Assuming an average amount of e-liquid consumed during 10 puffs (126.8 ± 12.1 mg), LOD and LOQ values correspond to

0.015 to 0.076 ng of substance emitted/mg of consumed e-liquid and 0.045 to 0.23 ng of substance emitted/mg of consumed e-liquid, respectively.

The accuracy of the method was determined by comparing the detector response after spiking 2 μL of standard solutions at two levels of 100 ng and 1000 ng on TD tubes, which were subsequently loaded by 10 puffs of analyte-free prepared e-liquid. The accuracy ranged between 91% and 110%, regardless of the spiking level.

The data obtained for the accuracy evaluation were used for the intra-day precision. The inter-day precision of the developed method was verified by the repeatable analysis (n=6) of TD tubes prepared as described on two abovementioned concentration levels over 3 days. The repeatability of the method was checked in terms of CV values and were not exceeding 10%. The accuracy and precision data are summarized in **Table 3.**

3.3. Analysis of real samples

To demonstrate that the method was fit for the purpose, eight commercially available e-liquid samples were evaluated for target analytes in the gas phase. The results are presented in **Table 4.**

The concentration of compounds detected in the gas phase represents only up to 0.15% of the total concentration of compounds in the aerosol, assuming the reported concentration of compounds in the liquid phase [27]. More than 99% of the substances are deposited mainly in the liquid phase of the aerosol. Only trace levels of analytes were detected in the gas phase. Generally, there was no strict relationship observed between the concentration of compounds in the e-liquid and their emission into the gas phase. However, some exceptions have been noticed. For example, in some cases, increased concentration of nicotine in the gas phase may be related to a high amount of this substance in the e-liquid as in "Tobacco" from brand B (e-liquid: 17.9 ± 0.9 mg/g, gas phase: 547-4472 ng/10puffs), while a low amount of nicotine corresponds to a lower amount in the gas phase as in "Strawberry" from brand A (e-liquid: 5.7 ± 0.2 mg/g, gas phase: 127-903 ng/10 puffs). This result agreed with the concentration levels of nicotine in the gas phase (64-253 ng/10 puffs) generated from the tested model e-liquid (nicotine concentration: 0.89 ± 0.05 mg/g). Similar relationships were observed for the other compounds such as isopentyl acetate. Such observation is not transferred to the other compounds such as, e.g., vanillin. The observed concentration of vanillin in the gas phase was in the range of 58-79 ng/10 puffs ("Vanilla" brand B, 2.07 ± 0.02 mg/g in e-liquid), and 51-364 ng/10 puffs ("Cherry'' brand D, 1.12 ± 0.04 mg/g in e-liquid). Despite this, for e-liquid "Cherry" from brand D (nicotine in e-liquid 5.4 ± 0.2 mg/g), the concentration of nicotine in

the gas phase was similar to the concentrations obtained for e-liquids with high nicotine content. Notably, the presence of menthol in the gas phase of e-liquids with menthol flavour and its absence in gas phase of model e-liquid may be explained by its high content in real samples of e-liquids analysed (above 7 mg/mL).

Observed variations in the emission factors may result from the differences in the e-liquid compositions (the PG and VG ratio) from different manufacturers, which may affect the partitioning of the compounds between the gas and liquid phase and make these reactions unpredictable.

4. Conclusions

In this work, a method using thermal desorption and GC-MS/MS was developed and validated for the determination of 34 compounds in the gas phase of aerosol generated from e-cigarettes. The hypothesis that the analytes are not only deposited in the liquid phase of aerosol and trace levels of them are transferred from e-liquid into the gas phase of the aerosol was confirmed. To accomplish this goal, the automatic generator of e-cigarette aerosol was applied to collect the gas phase of e-cigarette aerosol via TD tubes filled with Tenax TA. TD tubes were installed after a collection tube filled with 5*melt-blown* discs, which was previously used for evaluation of concentration levels of analytes in the liquid phase. This modification of the aerosol generator was simple to obtain and did not affect the aerosol collection. The results obtained supplement the data obtained previously. The key to the acquisition of reliable data was achieved by combination of non-woven *melt-blown* fabric with TD tubes and MCT approach. Both sampling media provide information about partitioning of target compounds in the generated aerosol. Even if the gas phase has a relatively small overall contribution and is composed primarily of ambient atmospheric species, the gas phase can immediately contact with the respiratory tract, as opposed to liquid-bound substances. Therefore, knowledge about changes in the distribution of liquid and gas phases is important to model the deposition in the lungs exactly.

Acknowledgments: none declared

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1. Concentration levels of analytes gas phase of an e-cigarette aerosol generated from model e-liquid spiked with target analytes at 1mg/mL. Consumed quantity e-liquid solution during one puffing session: 123.4 ± 5.1 (n=6).

Compound	Concentration ranges [ng/mg of consumed e-liquid]	Concentration ranges [ng/10 puffs]	Average concentration + SD [ng/mg of consumed e-liquid]	Average concentration + SD [ng/10 puffs]
Isopentyl acetate	33.5-40.9	4054-4970	36.5 ± 4.5	4551 ± 344
Leaf aldehyde	4.9-6.8	608-822	5.9 ± 0.8	740 ± 81
Isopentylisovalerate	<LOD	<LOD	<LOD	<LOD
Melonal	0.061-0.142	8.0-17.8	0.092 ± 0.038	11.3 ± 4.6
4-methyl-2-(1-methylethyl)-thiazole	<LOQ	<LOQ	<LOQ	<LOQ
n-Hexanol	<LOD	<LOD	<LOD	<LOD
cis-3-hexen-1-ol	<LOD	<LOD	<LOD	<LOD
2,3,5-trimethylpyrazine	<LOQ-0.162	<LOD-19.5	<LOQ-0.149 ± 0.018	<LOQ-18.2 ± 1.8
Trans-2-hexenol	<LOD	<LOD	<LOD	<LOD
Menthone (2 isomers)	<LOD	<LOD	<LOD	<LOD
Furfural	<LOD	<LOD	<LOD	<LOD
2,3,5,6-tetramethylpyrazine	<LOD-0.089	<LOD-10.7	<LOD-0.080±0.014	<LOD-9.7 ± 1.4
Theaspirane (2 isomers)	<LOD	<LOD	<LOD	<LOD
Benzaldehyde	<LOQ	<LOQ	<LOQ	<LOQ
L-menthyl acetate	<LOD	<LOD	<LOD	<LOD
Ethyl-3-methylthiopropionate	<LOD	<LOD	<LOD	<LOD
2-acetylpyridine	<LOD	<LOD	<LOD	<LOD
Menthol	<LOD	<LOD	<LOD	<LOD
Benzyl acetate	<LOD	<LOD	<LOD	<LOD
4-methylacetophenone	<LOD	<LOD	<LOD	<LOD
Benzyl alcohol	<LOD	<LOD	<LOD	<LOD
β-damascone	<LOD	<LOD	<LOD	<LOD
Methyl cyclopentenolone	<LOD-0.12	<LOD-14.4	<LOD-0.1149 ± 0.0015	<LOD-14.0 ± 0.5
Nicotine	0.47-2.15	63.7-252.8	1.17 ± 0.72	144 ± 87
Maltol	<LOQ-0.097	<LOQ-12.1	<LOD-0.09698± 0.00018	<LOD-11.86 ± 0.32
2-acetylpyrrole	<LOD	<LOD	<LOD	<LOD
Ethyl maltol	<LOQ-0.207	<LOQ-25.7	<LOQ-0.191±0.023	<LOQ-23.4 ± 3.4
γ-nonalactone	<LOD-<LOQ	<LOD-<LOQ	<LOD-<LOQ	<LOD-<LOQ
Furaneol	<LOD-0.197	<LOD-24.5	<LOD-0.188 ± 0.012	<LOD-23.0 ± 2.1
γ-decalactone	<LOD	<LOD	<LOD	<LOD
Eugenol	<LOD	<LOD	<LOD	<LOD
γ-undecalactone	<LOD	<LOD	<LOD	<LOD
Ethyl vanillin	<LOD-0.59	<LOD-72.9	<LOQ-0.45±0.22	<LOQ-54 ± 27
Vanillin	<LOD-0.74	<LOD-92.2	<LOQ-0.58± 0.27	<LOQ-71 ± 33

Table 2 Calculated numerical values of parameters describing the matrix-matched calibration curve, LOD, LOQ and correlation coefficients of the developed method

	Compound name	Calibration curve range (ng) (n=3)	Matrix matched calibration curve					LOD [ng]	LOQ [ng]	LOD [ng/mg of consumed e-liquid]	LOQ [ng/mg of consumed e-liquid]
			a	b	S_a	S_b	r				
1	Isopentyl acetate	10-2500	0.004761	0.026	0.000078	0.014	0.9982	9.6	29	0.076	0.23
2	Leaf aldehyde	10-2500	0.000928	-0.0007	0.000015	0.0026	0.9985	9.3	28	0.073	0.22
3	Isopentyl isovalerate	10-2500	0.01036	-0.004	0.00010	0.017	0.9992	5.5	17	0.043	0.13
4	Melonal	2.5-2500	0.008903	0.0000	0.000063	0.0057	0.9991	2.1	6.4	0.017	0.051
5	4-methyl-2-(1-methylethyl)-thiazole	2.5-2500	0.004498	0.0005	0.000031	0.0028	0.9990	2.1	6.3	0.017	0.051
6	n-Hexanol	10-2500	0.0002338	0.00030	0.0000014	0.00017	0.9994	2.4	7.1	0.019	0.057
7	cis-3-hexen-1-ol	10-2500	0.003446	-0.0028	0.000019	0.0034	0.9996	3.3	9.8	0.026	0.078
8	2,3,5-trimethylpyrazine	2.5-2500	0.003476	0.0004	0.000023	0.0021	0.9996	2	5.8	0.016	0.048
9	Trans-2-hexenol	10-2500	0.002232	-0.0007	0.000021	0.0037	0.9991	5.5	16	0.043	0.13
10	Menthone (2 isomers)	10-2500	0.003060	-0.0033	0.000037	0.0067	0.9990	7.2	22	0.057	0.17
11	Furfural	10-2500	0.001233	0.0017	0.000014	0.0024	0.9991	6.5	19	0.051	0.15
12	2,3,5,6-tetramethylpyrazine	2.5-2500	0.007680	0.0007	0.000061	0.0055	0.9994	2.4	7.2	0.019	0.057
13	Theaspirane (2 isomers)	10-2500	0.006184	-0.011	0.000087	0.016	0.9987	8.3	25	0.065	0.20
14	Benzaldehyde	2.5-2500	0.006541	-0.0148	0.000050	0.0045	0.9995	2.3	6.8	0.018	0.054
15	L-menthyl acetate	10-2500	0.003738	0.0058	0.000025	0.0046	0.9995	4	12	0.032	0.096
16	Ethyl-3-methylthiopropionate	10-2500	0.002833	-0.0046	0.000038	0.0068	0.9988	7.4	24	0.058	0.19
17	2-acetylpyridine	10-2500	0.004495	-0.005	0.000056	0.010	0.9989	7.4	22	0.058	0.17
18	Menthol	10-2500	0.001852	0.0058	0.000018	0.0032	0.9994	5.7	17	0.045	0.13
19	Benzyl acetate	10-2500	0.007403	-0.003	0.000070	0.013	0.9992	5.6	17	0.044	0.13
20	4-methylacetophenone	10-2500	0.01300	0.044	0.00013	0.024	0.9992	6.1	18	0.048	0.14
21	Benzyl alcohol	10-2500	0.0007023	0.00125	0.0000043	0.00077	0.9996	3.6	11	0.028	0.084
22	β-damascone	10-2500	0.0014347	0.0003	0.0000094	0.0017	0.9996	3.9	12	0.031	0.093
23	Methyl cyclopentenolone	2.5-2500	0.004829	0.0056	0.000036	0.0033	0.9990	2.2	6.7	0.017	0.051
24	Nicotine	10-5000	0.00575	0.0189	0.00019	0.0053	0.9990	3.0	9.1	0.024	0.072
25	Maltol	2.5-2500	0.002682	-0.0011	0.000019	0.0018	0.9990	2.2	6.5	0.017	0.051
26	2-acetylpyrrole	10-2500	0.01243	-0.013	0.00015	0.027	0.9990	7.2	21	0.057	0.17

27	Ethyl maltol	2.5-2500	0.001231	0.00132	0.000008	0.00071	0.9996	1.9	5.7	0.015	0.045
28	γ-nonalactone	2.5-2500	0.005861	0.0015	0.000046	0.0042	0.9991	2.4	7.0	0.019	0.057
29	Furaneol	2.5-2500	0.0004820	0.00117	0.0000032	0.00029	0.9993	2	6	0.016	0.048
30	γ-decalactone	10-2500	0.005812	0.0035	0.000051	0.0092	0.9994	5.2	16	0.041	0.13
31	Eugenol	10-2500	0.003419	0.0075	0.000029	0.0052	0.9994	5.0	15	0.039	0.12
32	γ-undecalactone	10-2500	0.005623	0.0074	0.000054	0.0097	0.9993	5.7	17	0.045	0.13
33	Ethyl Vanillin	10-2500	0.007302	0.009	0.000085	0.015	0.9991	6.9	21	0.054	0.17
34	Vanillin	10-2500	0.003893	0.0182	0.000054	0.0096	0.9989	8.2	24	0.065	0.19

Table 3 Repeatability and precision data for the developed method (n=6)

Compound name	Repeatability and precision				Inter- day precision			
	Spiking level							
	100 ng		1000 ng		100 ng		1000 ng	
	Accuracy [%]	CV [%]	Accuracy [%]	CV [%]	Accuracy [%]	CV [%]	Accuracy [%]	CV [%]
Isopentyl acetate	103	7	110	3	105	8	106	6
Leaf aldehyde	97	9	98	4	100	4	96	4
Isopentyl isovalerate	92	9	94	4	96	4	98	6
Melonal	98	9	102	4	99	4	103	3
4-methyl-2-(1-methylethyl)-thiazole	101	10	103	4	101	3	101	4
n-Hexanol	105	1	91	4	100	8	94	2
cis-3-hexen-1-ol	103	7	99	5	99	6	101	10
2,3,5-trimethylpyrazine	98	9	99	4	101	3	98	2
Trans-2-hexenol	104	7	103	5	100	6	99	6
Menthone (2 isomers)	91	6	103	4	97	6	104	1
Furfural	98	9	100	3	103	4	101	2
2,3,5,6-tetramethylpyrazine	94	9	95	4	97	2	94	3
Theaspirane (2 isomers)	90	5	106	6	93	4	103	3
Benzaldehyde	93	9	96	4	94	5	99	6
L-menthyl acetate	99	9	99	4	98	6	100	9
Ethyl-3-methylthiopropionate	94	9	97	4	98	4	101	4
2-acetylpyridine	93	2	98	3	95	2	97	1
Menthol	105	10	102	3	103	2	97	1
Benzyl acetate	95	10	96	4	95	3	100	3
4-methylacetophenone	107	10	112	4	105	7	108	6
Benzyl alcohol	100	9	101	4	103	2	99	2
β-damascone	98	9	99	5	99	3	99	0
Methyl cyclopentenolone	96	10	96	4	96	4	99	3
Nicotine	104	6	100	4	100	4	101	4
Maltol	93	6	97	4	99	7	97	1
2-acetylpyrrole	92	9	95	4	96	4	98	6
Ethyl maltol	92	4	110	3	101	8	105	8
γ-nonalactone	98	8	101	4	96	6	102	3
Furaneol	94	5	110	6	102	7	105	5
γ-decalactone	100	8	103	4	98	5	101	2
Eugenol	97	8	99	4	97	5	97	3
γ-undecalactone	102	8	103	4	100	5	102	1
Ethyl Vanillin	103	5	104	4	104	2	99	8
Vanillin	101	4	103	4	102	1	100	3

Table 4 Target analytes levels in gas phase of tested e-cigarette aerosols. Only detected substances were shown.

E-liquid description			Concentration ranges [ng/mg of consumed e-liquid]	Concentration ranges [ng/10 puffs]	Consumed quantity of e-liquid solution during one puffing session [mg ± SD (n=3)]
Brand	***Taste***	**Compound**			
A	Strawberry	Nicotine	1.2-8.8	127-903	107.7 +/- 4.2
B	Vanilla	Nicotine	7.53-11.61	934-1439	122.0 +/- 3.5
		Vanillin	0.34-0.40	58.4-78.9	
		Ethyl vanillin	0.47-0.64	40.2-49.7	
B	Menthol	Nicotine	6.9-20.6	985-2805	138.7 +/- 3.1
		Menthol	<LOD-<LOQ	<LOD-<LOQ	
C	Crisp mint	Nicotine	0.43-8.5	58-1031	132.3 +/- 10.3
		Menthol	<LOD-<LOQ	<LOD-<LOQ	
D	Cherry	Nicotine	6.6-17.1	715-2140	119.0 +/- 12.5
		Vanillin	0.46-3.16	50.5-363.8	
		Isopentyl acetate	3.2-4.6	426-527	
		Benzaldehyde	<LOQ	<LOQ	
C	Apple	Nicotine	0.63-11.25	42-1519	113.7 +/- 9.1
		Leaf aldehyde	0.179-0.245	24.9-33.1	
		Isopentyl acetate	2.4-3.4	339-457	
B	Black Tea	Nicotine	2.5-17.8	353-2455	138.7 +/- 3.1
		Benzaldehyde	<LOQ-0.071	<LOQ-9.8	
B	Tobacco	Nicotine	4.5-33.4	547-4472	131.3 +/- 8.3
		Ethyl maltol	<LOD-0.104	<LOD-13.8	
		Methyl cyclopentenolone	<LOD-0.173	<LOD-23.2	