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An online method for the analysis of volatile organic compounds in electronic cigarette aerosol based on proton transfer reaction mass spectrometry

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RATIONALE: Due to the recent rapid increase in electronic cigarette (e-cigarette) use worldwide, there is a strong scientific but also practical interest in analyzing e-cigarette aerosols. Most studies to date have used standardized but time-consuming offline technologies. Here a proof-of-concept for a fast online quantification setup based on proton transfer reaction mass spectrometry (PTR-MS) is presented.

METHODS: The combination of a novel sampling interface with a time-of-flight PTR-MS instrument specially designed for three scenarios is introduced: (i) mainstream aerosol analysis (aerosol that the user inhales prior to exhalation), and analysis of exhaled breath following (ii) mouth-hold (no inhalation) and (iii) inhalation of e-cigarette aerosols. A double-stage dilution setup allows the various concentration ranges in these scenarios to be accessed.

RESULTS: First, the instrument is calibrated for the three principal constituents of the e-cigarettes' liquids, namely propylene glycol, vegetable glycerol and nicotine. With the double-stage dilution the instrument's dynamic range was easily adapted to cover the concentration ranges obtained in the three scenarios: 20–1100 ppmv for the mainstream aerosol characterisation; 4–300 ppmv for the mouth-hold; and 2 ppbv to 20 ppmv for the inhalation experiment.

CONCLUSIONS: It is demonstrated that the novel setup enables fast, high time resolution e-cigarette studies with online quantification. This enables the analysis and understanding of any puff-by-puff variations in e-cigarette aerosols. Large-scale studies involving a high number of volunteers will benefit from considerably higher sample throughput and shorter data processing times. © 2016 The Authors. *Rapid Communications in Mass Spectrometry* Published by John Wiley & Sons Ltd.

Searching for the term "electronic cigarette" in Google Scholar^[1] reveals about 340 hits for the year 2012, 510 hits for 2013, 940 hits for 2014 and already 850 hits for the first eight months of 2015 (patents and citations excluded). This reflects the increasing scientific and also general interest in this topic, which is probably driven by the rapid worldwide increase in electronic cigarette ("e-cigarette") use by adult smokers.^[2,3] The setup and working principle of a typical e-cigarette have been described elsewhere (e.g. ^[4]). In short, these are battery-powered devices that convert a liquid ("e-liquid") into an aerosol (often but inaccurately called "vapour"), which can be inhaled or held in the mouth (no inhalation) by the user prior to exhalation (for details on the

terminology, see Table 1). E-liquids typically contain defined amounts of nicotine and flavourings in a base matrix consisting of propylene glycol and/or vegetable glycerol.^[5] E-cigarettes deliver nicotine without the combustion of tobacco and are often marketed as an alternative to conventional cigarettes.^[5] Given the increase in e-cigarette use there is a growing interest from regulators and public health organizations to understand the potential implications of e-cigarettes from a consumer and bystander perspective.

One recent and very comprehensive e-cigarette study has been published by Geiss *et al.*^[6] The authors analyzed different e-liquids containing different flavours, with varying nicotine content. Furthermore, the authors investigated the composition of the mainstream aerosol produced by e-cigarettes and the impact that the use of these e-cigarettes ("vaping") had on air quality in a 30 m³ emission chamber. They used conventional, i.e. gas chromatography (GC)- and high-pressure liquid chromatography (HPLC)-based methods for the quantification of nicotine, propylene glycol, glycerol, flavourings and volatile carbonyl compounds in e-cigarette aerosol. A review of the literature shows that most e-cigarette studies use these analytical methods (e.g. ^[7–10]), probably due to the status of

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Table 1. Terminology of the scenarios in this work

Scenario	Description
Mainstream aerosol	The aerosol which is produced by the e-cigarette and is inhaled by the user via the e-cigarette's mouthpiece.
Inhalation	Exhaled breath after the user has inhaled mainstream aerosol into the lungs.
Mouth-hold	Exhaled breath after the user has kept the mainstream aerosol in the mouth but has not inhaled it.

GC and HPLC as convenient and cost-effective "gold standard" techniques in analytical chemistry. The advantages of these technologies are well known; however, they do have certain drawbacks when used in e-cigarette research. For example, when Geiss *et al.* analyzed the e-cigarette mainstream aerosol, a condensate of 13 puffs was collected on a glass fibre filter pad, extracted with 2-propanol, filtered then analyzed utilizing GC coupled to a flame ionisation detector (GC-FID). Such a process is labour intensive and time consuming, particularly when a series of different puff topographies has to be analyzed. (In this context, the term topography is used to define the consumption behaviour of the user; how a person vapes, puff numbers, volume and duration.) Moreover, analysis on a per-puff basis cannot be achieved. When Behar *et al.*^[11] quantified the nicotine intake for variable vaping topographies of e-cigarette users, they applied a "pseudo-online" method rather than carrying out separate GC-FID analyses for a vast amount of puff topographies. The e-cigarette component that contains the e-liquid and vaporization unit (so-called "cartomizer") was weighed before and after each experiment. From the difference in mass and the nicotine concentration in the e-liquid (as stated on the label and from a separate HPLC analysis) the nicotine intake by the users was calculated. Whereas this method might be a feasible option for calculating average nicotine delivery, only a true online puff analysis can consider any puff-by-puff variations and effects caused, e.g., by extreme puff topographies (cf. ^[12]) or the cartomizer running dry. Moreover, Geiss *et al.* noted that the nicotine concentrations that they measured in the vapour condensate were not always proportional to the concentrations in the e-liquids.

Recently, Blair *et al.*^[13] published a method for the real-time quantification of volatile organic compounds (VOCs) in e-cigarette aerosols and other types of tobacco-containing cigarettes. For the study they utilized a Proton Transfer Reaction Mass Spectrometry (PTR-MS) instrument with a fast-flow tube front end and focused on the quantification of compounds formed from the heating of the e-liquid: acetaldehyde, acetone, acetonitrile, acrolein and methanol. The authors did not quantify the levels of propylene glycol, vegetable glycerol or nicotine – the principal components of e-liquids. Importantly, their study demonstrated that PTR-MS can be a powerful tool for the real-time and online analysis of e-cigarette aerosols.

Although PTR-MS is commonly used in environmental chemistry,^[14] food science,^[15] medical research^[16] and threat compound and drug detection applications,^[17,18] one of the first publications ever based on PTR-MS data in 1995, i.e. three years before the first instruments became commercially available, was a comparison between chemicals released in the exhaled breaths of smokers and non-smokers by Jordan *et al.*^[19] That is, the potential of PTR-MS for the online analysis of cigarette VOCs has already been noted in its early

prototype stage. For a comprehensive overview on PTR-MS applications and publications, see Ellis and Mayhew.^[20]

We published a study on nicotine concentrations in exhaled breath following use of e-cigarettes under different vaping topographies using PTR-MS.^[21] However, in that first proof-of-concept study we used a generic PTR-MS inlet system and thus we were confronted with two major difficulties. As PTR-MS has been invented for the extremely sensitive quantification of trace gases, it is ideally suited for the analysis of the low nicotine concentrations that have been observed in exhaled breath following inhalation of e-cigarette aerosol. Given the high sensitivity of the PTR-MS instrument, for the analysis of exhaled breath after the user kept the aerosol in the mouth but did not inhale ("mouth-hold"), the concentrations were exceeding the upper dynamic range limit of the PTR-MS instrument; thus, sample dilution was necessary. In our first study we performed this dilution by simply adding purified air to the inlet flow into the instrument, which was sufficient for the mouth-hold topography, but not for the mainstream e-cigarette aerosols. For that reason, a GC-FID method was employed for this part of the analysis. Furthermore, the sampling interface consisted of a simple 1/4 inch T-piece with the PTR-MS inlet positioned in its centre, which led to some memory effects because of condensation.

Here we present a novel sampling setup for PTR-MS instruments that overcomes virtually all these difficulties. All concentration regions can be accessed via a double-stage dilution system, i.e. inhalation, mouth-hold and mainstream aerosol experiments can be performed with the same setup by simply changing the dilution flows. In addition, the sampling interface has been designed in a completely new way, so that condensation is prevented, memory effects are kept low and disposable mouth-pieces for breath analysis as well as an adapter for e-cigarette mainstream analysis can be mounted. With this setup it is possible to perform all types of e-cigarette research online, i.e. puff-by-puff analyses with a high time resolution.

EXPERIMENTAL

The PTR-MS technology has been described in detail elsewhere.^[20] For this study a PTR-TOF 8000 was used (IONICON Analytik GmbH, Innsbruck, Austria), which is a time-of-flight (TOF) mass spectrometry based instrument. A sensitivity of about 100 cps/ppbv (ion yield in counts-per-second/concentration) at m/z 79 has been determined for this instrument, which increases with increasing m/z up to about 210 cps/ppbv at m/z 147.^[22] Although equipped with the capability to choose between H_3O^+ , NO^+ , O_2^+ and Kr^+ as reagent ions,^[23] the instrument was operated here exclusively in H_3O^+ mode, where water vapour is converted into hydronium reagent ions in the hollow cathode ion source. The drift tube, where

proton transfer occurs to all VOCs that possess a higher proton affinity (PA) than water (691 kJ/mol^[24]), was operated at about 130 Td (Townsend; 1 Td = 10⁻¹⁷ cm² V), which corresponds to a drift tube pressure of 2.3 mbar, drift tube temperature of 120 °C and drift tube voltage of 500 V.

Concentration calibration

The PTR-MS instrument was calibrated for the three principal constituents of e-liquids: propylene glycol (PG; C₃H₈O₂; 99.5%; Brenntag Ltd, Leeds, UK), vegetable glycerol (VG; C₃H₈O₃; 99.5%; Brenntag Ltd; PA = 874.8 kJ/mol^[24]), nicotine (C₁₀H₁₄N₂; 7.2% in PG; Nicobrand, Coleraine, UK; PA = 963.4 kJ/mol^[24]). Although PTR-MS allows for quantification without calibration,^[25] for PG and VG, a calibration is inevitably required because of their high fragmentation rate even upon the relatively "soft" PTR ionisation. A calibration was also performed for nicotine in order to increase accuracy. As PTR-MS only analyses gaseous compounds, a liquid calibration unit (LCU; IONICON Analytik GmbH; for details, see Fischer *et al.*^[26]) was utilized to convert aqueous solutions of PG, VG and nicotine into vapours with well-defined compound concentrations.

Sampling setup

The three scenarios in e-cigarette analysis for which the sampling setup was designed are: (i) mainstream aerosol analysis, and analysis of exhaled breath following (ii) mouth-hold (no inhalation) and (iii) inhalation of e-cigarette aerosols.

Probably the most important requirement when a user has to exhale into an analytical device is that the mouthpiece has to be disposable, i.e. hygiene criteria have to be fulfilled. Furthermore, there should be measures installed that prevent the exhaled breath from being inhaled again. Common mouthpieces that are used in alcohol breathalyzer tests fulfil both criteria. Thus, we designed our sampling interface so that one of these mouthpieces (EnviteC-Wismar GmbH, Wismar, Germany) can be used and easily exchanged.

Sampling mainstream aerosol is somewhat more complicated, as the e-cigarette is connected to a smoking machine to activate the device and generate the aerosol. A smoking machine is a device that holds a cigarette and automatically executes puffs with adjustable well-defined durations, volumes and intervals. For our experiments we utilized a linear smoking machine (LX1; Borgwaldt GmbH, Hamburg, Germany). Although these types of smoking machines have been designed for conventional cigarettes, they have successfully been adapted to operate e-cigarettes.^[21] GC analysis of cigarette smoke or e-cigarette aerosol is performed by installing a filter pad and/or impinger between the (e)-cigarette and the smoking machine, so that compounds are trapped on the filter pads or in the impingers, which are subsequently analyzed. Online analysis with PTR-MS requires a constant airflow; thus, sampling at this position would not be feasible, because the airflow would interfere with the smoking machine's puffing procedure. Another possible sampling point would be the exhaust port of the smoking machine. However, this means that no glass filter pad can be installed between the e-cigarette and the smoking machine and that unfiltered aerosol passes through the device. This risks damaging the smoking machine or at least severely contaminating all lines, the pump piston and valve, which are at room temperature and not made of inert materials.

Consequently, concentrations in the exhaust stream are diminished and an extremely high background signal is observed. We found that the best solution for sampling mainstream e-cigarette aerosol is to reverse the airflow of the smoking machine, which can be achieved by simply exchanging the lines to the cigarette and exhaust port. As an e-cigarette does not involve any combustion, but is activated by airflow, it can be inserted into the cigarette port with its tip ahead, so that the aerosol is ejected out of the e-cigarette's mouth piece end directly into the sampling interface. With this configuration the smoking machine does not come into contact with the aerosol, i.e. stays perfectly clean, and sampling can be easily performed.

The insert in Fig. 1 shows the sampling interface. The outer housing, which is mounted directly at the heated inlet hose of the PTR-MS instrument, is made out of aluminium, about 8 cm long and 2 cm wide. Close to the mounting point a 1/4 inch tubing, which is connected to an orifice in the outer housing and via a needle valve to the bypass port of the internal membrane pump of the PTR-MS instrument, creates a constant airflow of about 500 sccm (standard cubic centimetre per minute) through the interface. This airflow should ensure that the interface is continuously flushed and build up of contamination is avoided. When breath needs to be sampled, one of the above-mentioned disposable mouthpieces can be plugged into the housing. In order that users can exhale freely into the interface, a small membrane is mounted on top of an orifice in the outer housing. This membrane acts as a one-way valve, so that no outside air is admixed to the sample at this point, but excess air is expelled. In the case of the mainstream aerosol, the mouthpiece is exchanged with a small funnel, which ensures that the aerosol generated by the smoking machine is efficiently guided into the interface. The actual sampling is performed via a passivated stainless steel tube (1 mm i.d.) in the central axis of the aluminium housing. Similar to known designs in thermodesorption units (e.g. ^[27]) a heating wire is wrapped around this tube, so that it can be heated up to approximately 200 °C (measured via a thermocouple temperature sensor). For the measurements presented in the Results section we used a temperature of 170 °C. The tube is connected directly

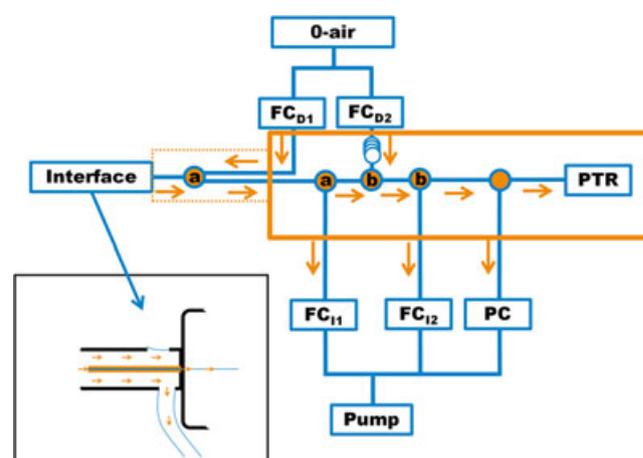


Figure 1. Schematic representation of the e-cigarette aerosol sampling inlet system; the arrows indicate the air flow; for details see text. The sampling interface is shown in the insert on the bottom left. FC, mass flow controller; PC, pressure controller.

to the heated PTR-MS inlet system without any cold spots, so that condensation is avoided. Although the PTR-MS inlet system was heated to 120 °C we did not observe any condensation effects in the transition zone between the interface and the inlet system, which is probably because the aerosol is vaporised in the interface and shows a much lower tendency to condense in this gaseous state.

Double-stage dilution/inlet setup

The upper limit of the dynamic range of a PTR-MS instrument is commonly determined via the depletion of reagent ions upon sample introduction.^[25] One way of doing this is by comparing the ion yields of $\text{H}_3^{18}\text{O}^+$ (m/z 21; the ion yield for H_3O^+ overloads the detector) during the introduction of zero-air and air containing the VOCs. If reagent ion depletion is more than about 10% the VOC concentration is too high and sample dilution is required. As we were expecting a very broad concentration range for the three sampling scenarios (inhalation, mouth-hold and mainstream aerosol), we developed a double-stage dilution setup, which is schematically displayed in Fig. 1.

First, it should be noted that all lines and T-pieces (represented as filled circles) used in this setup are made of PEEK (Polyether ether ketone). The dotted rectangle represents the 1.2 m heated (120 °C) inlet hose (Gummi-Winkler GmbH, Rum, Austria) which connects the sampling interface with the PTR-MS instrument. The hose can hold up to four 1/16 inch capillaries and is equipped with a heated (120 °C) cylindrical box at one end. This box can hold a Y-piece and its front plate provides space for mounting the sampling interface. The other end of the hose is connected to the heated (120 °C) inlet chamber (solid rectangle) of the PTR-TOF 8000.

The functional principle of the double-stage dilution setup can be explained in two single stages, indicated by the letters "a" and "b" on the relevant T-pieces in Fig. 1. Both stages work the same way; that is, a suction gas flow is created by a pump (membrane pump already installed in the PTR-TOF 8000) and controlled by a mass flow controller (FC; indices are for identification of the respective FC). Via a second FC, which is fed by pressurized air from a zero-air generator, purified air is injected into the suction flow. As long as the flow rate of the suction flow is higher than the flow rate of purified air, the result will be a suction flow at the mixing T-piece, which can be used for sampling. As an example for dilution stage "a": If FC_{11} is set to 200 sccm and FC_{D1} to 150 sccm, the sampling flow will be 50 sccm and the dilution factor (DF) will be 4, i.e. the actual concentration of the sample gas can be calculated by multiplying the concentration in the diluted gas by 4. The same applies for stage "b": If FC_{D2} is set to 400 sccm and FC_{12} to 390 sccm, the sampling flow will be 10 sccm and the DF will be 40. As the sample gas of stage "b" is the already diluted gas from stage "a", these two DF values have to be multiplied to obtain the overall DF. What makes things somewhat more complicated is that in this case the 10 sccm sampling flow from stage "b" creates an additional suction in stage "a", i.e. 210 sccm are drawn into the instrument and the real DF of stage "a" is 3.5, resulting in an overall DF of 140.

It is noteworthy that the zero-air should be heated to the same temperature as the rest of the inlet system prior to mixing it with the sample gas, as cold zero-air may lead to

condensation at the mixing point. In stage "a" this is achieved by feeding the zero-air capillary through the 1.2 m inlet hose. In stage "b" about 1.5 m of the zero-air capillary is coiled up inside the heated inlet chamber prior to the mixing point. Furthermore, the above-mentioned example does not take into account that after stage "b" there still is the PTR drift tube and a pressure controller (PC), which is necessary to adjust the pressure in the drift tube. Together they create an additional suction flow in the inlet system, which again influences the DF. Therefore, in order to determine the exact DF we use a simple experimental method (which is described in the following paragraph) rather than performing complex calculations based on readings of FCs, which introduce unknown inaccuracies.

The PTR-TOF 8000 has been shown to give a linear instrumental response over a concentration range of at least five orders of magnitude.^[22] Thus, for calibrating the DF of a set dilution, a polypropylene bag is filled with air containing traces of a known volatile substance and the bag is connected to the sampling interface, so that exclusively the content of the bag is sampled by the instrument. Subsequently, the zero-air supply is turned off by setting FC_{D1} and FC_{D2} to 0 sccm, i.e. set the DF to 1. By comparing the ion yields of the protonated molecule of the "calibration" compound under both conditions (with and without dilution), the DF is obtained. Limonene has been shown to be a good example for such a calibration compound as it is non-toxic and readily available. In addition, its vapour pressure (2.04 mbar at 20 °C^[28]) is already sufficiently high at room temperature, so that limonene headspace can be directly added to the bag without the need for heating.

The main advantage of this double-stage dilution system is that high DFs of up to 5000 can be reached, while no modifications of the PTR-TOF 8000 inlet chamber are necessary, i.e. all capillaries and T-pieces easily fit into the given space. In addition, the sample gas does not come into contact with any valves, FCs or PCs prior to entering the PTR drift tube. The only material that the gas comes into contact with is PEEK; thus, contaminations and memory effects are suppressed. It has to be mentioned that diluting the sample increases not only the upper limit of the instrument's dynamic range, but also the lower limit. Therefore, the limit of detection, which has recently been reported to be between 2.8 and 145 pptv for dwell times of 60 s and 0.1 s, respectively, for the PTR-TOF 8000,^[22] also has to be multiplied by the DF. This could lead to problems when very low concentration compounds have to be detected in the e-cigarette aerosol (e.g. flavour compounds) and will be the subject of further studies.

E-cigarettes for testing

For testing and evaluating our novel setup we used a commercially available e-cigarette (JAI; Fontem Ventures B. V., Amsterdam, The Netherlands) with a tank system – a model where the e-liquid can be (re-)filled by the user. The e-liquid composition was PG 68%, VG 30%, nicotine 1.8% (w/w) and flavour mix. The battery was fully charged prior to conducting each measurement.

The *in vivo* tests were performed by one adult smoker who was an experienced e-cigarette user. We limited the number of e-cigarette models and volunteers to one, as the aim of this

study was neither a comparison of different e-cigarette models nor to assess inter-subject variability, but to introduce the novel sampling setup.

RESULTS

The calibration plots obtained using the LCU for PG, nicotine and VG are displayed in Figs. 2(a), 2(b) and 2(c), respectively. The y-axes represent the concentrations of the respective compound in the gas phase in ppbv. The x-axes represent the obtained ion yields of the protonated molecules in ncps

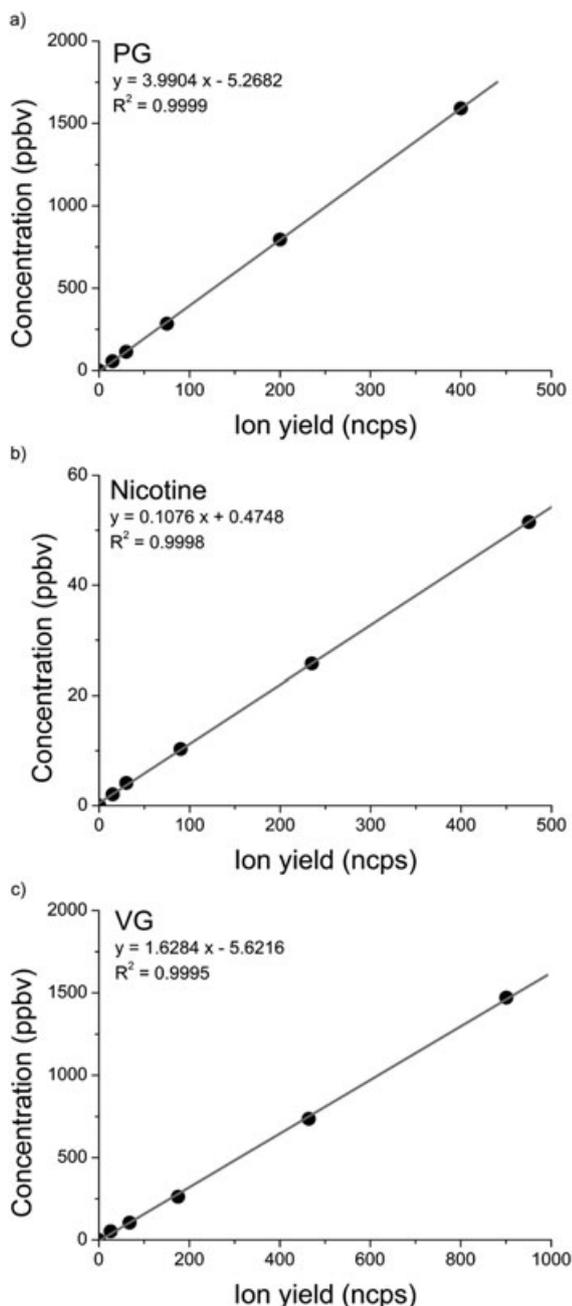


Figure 2. Calibration plots for (a) propylene glycol (PG), (b) nicotine, and (c) vegetable glycerol (VG) including the corresponding calibration functions, which have been derived from linear fits of the data points.

(normalized counts per second; normalized to 1×10^6 H_3O^+ reagent ions). The solid lines are linear fits of the data points (filled circles), with the corresponding fitting functions stated in the upper left of each diagram. Where a dilution was applied in measurement, the calculated concentration values have to be multiplied by the DF.

With these calibration functions we are able to directly convert the measured ion yields in ncps into concentration values in ppbv, i.e. we get an online reading of compound concentrations in the e-cigarette aerosol. In order to test this functionality over a broad range of concentrations, we analyzed the mainstream aerosol of an e-cigarette connected to the smoking machine and volunteer-exhaled breath after mouth-hold and inhalation topographies of e-cigarette aerosols, respectively. Representative results for PG, nicotine and VG in these three scenarios are shown in Figs. 3–5. The total time-span for all the graphs presented here is 400 s, although every data point has been integrated for only 390 ms to get a high time resolution. For the mainstream aerosol test, which is shown in the upper panel (a) of each figure, we set the smoking

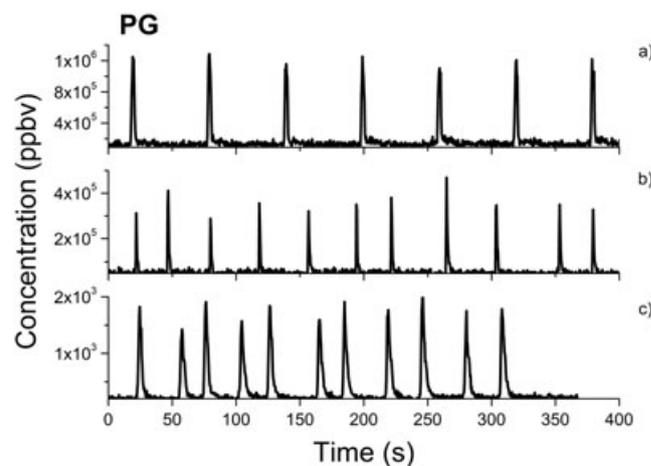


Figure 3. Concentrations (ppbv) of PG measured (a) in the mainstream aerosol, (b) exhaled after aerosol mouth-hold, and (c) exhaled after aerosol inhalation. Note the different orders of magnitude for the concentration axes.

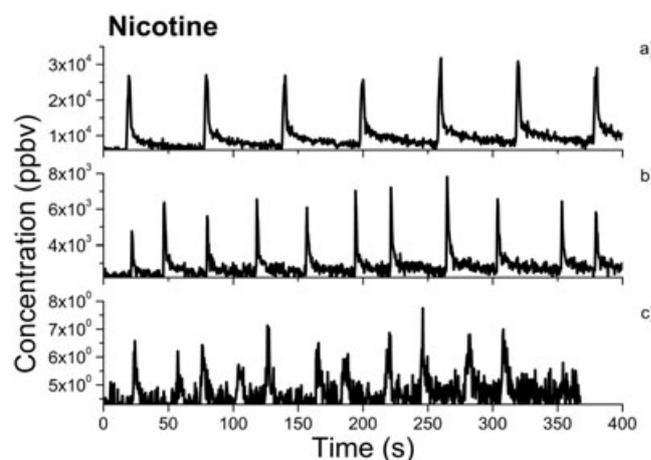


Figure 4. Concentrations (ppbv) of nicotine measured (a) in the mainstream aerosol, (b) exhaled after aerosol mouth-hold, and (c) exhaled after aerosol inhalation. Note the different orders of magnitude for the concentration axes.

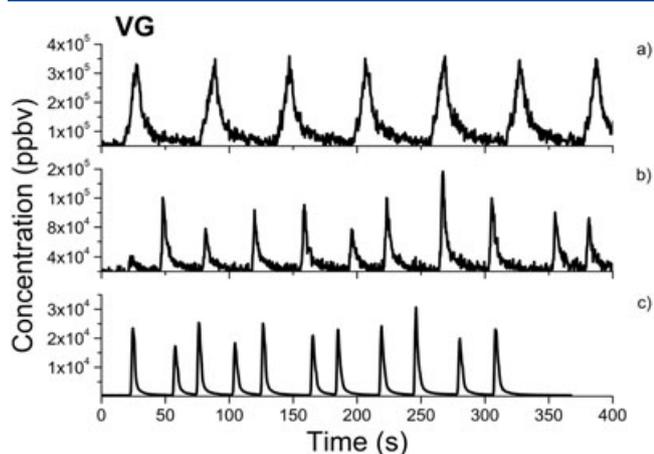


Figure 5. Concentrations (ppbv) of VG measured (a) in the mainstream aerosol, (b) exhaled after aerosol mouth-hold, and (c) exhaled after aerosol inhalation. Note the different orders of magnitude for the concentration axes.

machine to 60 mL puff volume, 3 s puff duration and 60 s puff interval. A first strong indicator that contamination is avoided is that within the 60 s interval the concentrations return to baseline levels; none of the three compounds accumulate in the sampling system. This is in contrast to previous experimental designs tested. Particularly for nicotine and VG a build-up of the signal background was observed after each puff, leading to "staircase like" concentration readings. Furthermore, for PG and nicotine the time from the onset of the signal peaks to the beginning of the decrease corresponds very well to the puff duration (about 2.5 s for 3 s duration; note that the e-cigarette needs some time to activate and heat up the coil to aerosolise the e-liquid), which is an indicator that the aerosol is analyzed in real-time. However, for the compound with the lowest vapour pressure, VG, we see a broadening of the peaks in this high concentration regime. This has to be taken into account when working with VG concentration values, as they probably are somewhat underestimated. Averaging the maximum concentration values of all seven puffs and subtracting the baseline concentrations results in values of 1063 ppmv (78% of the sum of all three compound concentrations) for PG, 23 ppmv (2%) for nicotine and 270 ppmv (20%) for VG, which seems plausible compared with the composition of the e-liquid. Furthermore, in our recent study,^[21] where we used the same smoking machine but two different types of e-cigarettes with 2% nicotine content, GC-FID analysis of 15 puffs for 3 s each gave a concentration of 15–20 ppmv/puff nicotine, which confirms our present online measurements.

For the mouth-hold analysis, the volunteer was asked to perform "free vaping", i.e. puff volume, puff duration, mouth-hold duration and puff interval could be varied according to the volunteer's natural topography. This means that the compound concentrations are not directly comparable with the mainstream aerosol values, as not necessarily the same amounts were delivered to the mouth. The results are shown in the middle panels (b) of Figs. 3–5. Again, even for short puff intervals of below 30 s, the baseline levels are reached for all three compounds prior to the following puff. For PG concentration values around 300 ppmv (78%), for nicotine around 4 ppmv (1%) and for VG

around 80 ppmv (21%) were measured (averages of maxima for all puffs, baseline subtracted), i.e. a similar composition to that in the mainstream aerosol with a slightly reduced relative nicotine abundance.

The inhalation test yields by far the lowest concentration values, probably because of a high retention rate of the investigated components. Similar to the mouth-hold study, the volunteer was given full freedom concerning puff volume, puff duration, inhalation depth and puff interval. The results are shown in the lower panels (c) of Figs. 3–5. From conventional cigarette studies it is known that, following inhalation of tobacco smoke, the nicotine retention rate is >99%.^[29] For the retention of nicotine, following inhalation of e-cigarette aerosol, we recently also obtained a value of >99%.^[21] Thus, it is not surprising that here, following inhalation of e-cigarette aerosol, the exhaled breath contained only about 2 ppbv (<<1%) nicotine (average of maximum values, baseline subtracted). Although the nicotine concentration is four orders of magnitude lower than that of the most abundant compound, VG (22 ppmv, 93%), and the integration time is only 390 ms, the signal can still be well separated from the background noise level. The average maximum PG concentration was about 1.6 ppmv (7%).

CONCLUSIONS

We have developed a novel sampling setup for the analysis of both mainstream and exhaled e-cigarette aerosols based on PTR-MS. The main parts of the setup are a heated interface designed for mainstream aerosol and exhaled breath analysis and a double-stage dilution system for shifting the dynamic range of a PTR-MS instrument up to extremely high concentrations. After determining calibration functions for the three most abundant compounds in e-liquid (PG, VG and nicotine), we tested the setup for three scenarios, namely mainstream aerosol and exhaled breath following mouth-hold, and inhalation of the mainstream aerosol by an experienced e-cigarette user. The concentration ranges that we found in these scenarios were spread over a wide range of concentrations: 20–1100 ppmv for mainstream, 4–300 ppmv for mouth-hold and 2 ppbv to 20 ppmv for inhalation. However, the double-stage dilution system made all these ranges easily accessible and e.g. the mainstream aerosol nicotine quantification value is in very good agreement with that in our recent GC-FID study. For PG and nicotine we found excellent correlation between the instrumental response and the puff duration, indicating a true online measurement. Only for VG and concentrations greater than about 100 ppmv did we find some broadening of the concentration peaks.

We propose that with this setup a broad variety of online puff-by-puff e-cigarette studies will be possible which is important for the evaluation of e-cigarettes from both a consumer and a bystander perspective. For example, the impact of changing e-cigarette device parameters such as voltage and battery power on aerosol composition could be analyzed in real-time on a puff-by-puff basis. Another example could be a study involving a large group of volunteers, where differences in compound concentration in exhaled breath can be related to vaping topographies. Our setup will be particularly suitable for such a broad study, as the analysis and data evaluation processes are very fast. As

e-cigarettes are gaining regulatory and public health interest the combination of our novel inlet setup and PTR-MS will be an ideal tool for scientific research in this field.

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