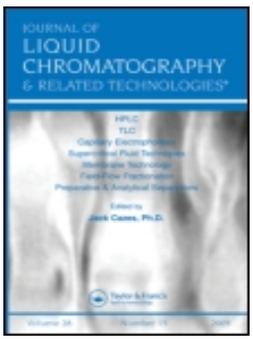

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No Quantifiable Carbonyls, Including Formaldehyde, Detected in Voke® Inhaler

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Carbonyls such as formaldehyde, acetaldehyde, and acrolein have been detected in e-cigarette vapors, with one study (albeit at a higher than the typical voltage) reporting formaldehyde-releasing agents in quantities sufficient to increase the risk of cancer by 5–15 fold when compared with long-term smoking. This study examines the Voke® Inhaler for traces of carbonyls and aims to quantify any that are detected in its aerosol. Three batches of five Voke® devices each were charged with formulation and allowed to rest for 0, 1, and 24 hr respectively, before being sampled. Aerosol from each device was extracted using a linear smoking machine and collected by dissolution into DNPH derivatization solution. Samples of the extract solution were analyzed for carbonyls using UHPLC. Results were reported as µg/8 puffs. Samples were analyzed for the presence of formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, butan-2-one, and butyraldehyde. At the given LOD, no carbonyls were detected in 13 of the 15 samples tested. Acetaldehyde was detected in two samples, one tested immediately after charging and the other tested 1 hr after sampling; however, both samples contained the analyte in quantities below its LOQ (3.18 µg/mL). Among various carbonyls, formaldehyde, in particular, has been identified as a known carcinogen by the IARC and as a probable human carcinogen by the US EPA. The absence of measurable quantities of carbonyls in the Voke® Inhaler establishes its clear distinction from e-cigarettes and reflects on a significant advantage of not having a heating element.

Keywords: carbonyls, formaldehyde, Voke® Inhaler, e-cigarette, acetaldehyde and thermal degradation

Introduction

Smoking harm reduction is becoming an increasingly widespread health campaign owing to the growing burden of diseases caused by tobacco smoking. Despite the fact that many smokers make attempts to quit, only 0.5%–5% of them achieve lasting abstinence without help or support, while the remaining relapse due to their dependence on nicotine.[1] A number of licenced Nicotine Replacement Therapy (NRT) products have been designed to help motivated smokers cut down and quit (i.e., smoking cessation) as well as reduce the harm to the users and those around them; these products include nicotine patches, nicotine gums, nicotine lozenges, nicotine sprays, and nicotine sub-lingual tablets all of which provide nicotine to the user without delivering carcinogens generated during tobacco combustion in cigarette smoking. However, studies have indicated that NRTs may not be as effective as expected and that relapse rates with or without NRTs are comparable.[2] This may, in part, be due to the lack of behavioral and social components of smoking with use of these products. The desire for alternative formats of nicotine delivery products has been shown by the emergence of e-cigarettes–battery powered electronic nicotine delivery devices (ENDs).[3]

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E-cigarettes are hand-held devices containing nicotine formulations that are vaporized by battery-powered heating elements. They are designed for the purpose of providing a nicotine containing vapor to the user, besides which they also provide smoking associated cues such as the hand-to-mouth ritual and presence of an exhaled vapor. Their worldwide increase in trial and usage has resulted in a demand for substantive safety and efficacy data by both consumers and regulatory authorities. As a result, the European Tobacco Product Directive (TPD) was revised in April 2014 to regulate nicotine containing products, including e-cigarettes. As per its guidelines, any e-cigarette product containing up to 20 mg/mL of nicotine would qualify in the TPD e-cigarette category while those with higher concentrations would require to be licenced as a pharmaceutical to be placed on the market.[4] Among the various requirements of the revised TPD, one is the provision of a list of all ingredients contained not only in the product formulation (e-liquid) but also in the emissions resulting from their use; furthermore, these ingredients would need to be quantified as well as toxicologically assessed.[5]

Formaldehyde and other carbonyls, VOCs, and tobacco specific nitrosamines have been detected in e-cigarette cartridges and vapors.[6–8] One study quantified formaldehyde-releasing agents in e-cigarette vapors and concluded that if these agents were assumed to carry the same risk per unit of formaldehyde as the risk associated with inhaling gaseous formaldehyde, then long-term "vaping" is associated with an incremental lifetime cancer risk that could be 5–15 times as high as the risk

associated with long-term smoking.[9] These compounds are understood to be released as a result of thermal decomposition of e-liquids. Formaldehyde has been identified as a known carcinogen by the International Agency for Research on Cancer (IARC)[10] and as a probable human carcinogen by the US Environmental Protection Agency (US EPA).[11]

Voke® is a pharmaceutically regulated HFA-based Nicotine Inhaler developed by Kind Consumer Ltd. and Nicovations Ltd. for use in relieving and/or preventing craving and nicotine withdrawal symptoms. It is a non-electronic, breath-operated delivery system that delivers a pressurized inhalation solution containing nicotine to the respiratory system and is indicated as a safer alternative to smoking for smokers and those around them.[12] The purpose of this study was to assess the Voke® formulation, and the aerosol it delivers, for the presence of formaldehyde and other carbonyl compounds, and quantify them if necessary.

Methods

Samples

The test samples were Voke 0.45 mg Inhaler products that comprise a refillable device and a pressurized canister containing nicotine formulation. Each canister provides the device with approximately 20 charges of formulation (a solution of nicotine (0.056% w/w) comprising ethanol and propylene glycol as the co-solvents, HFA propellant, and menthol and saccharin as flavoring excipients).

For the purpose of this testing, 15 inhalers were prepared as follows:

- Batch 1: Five Voke® devices were charged with formulation and tested immediately.
- Batch 2: Five Voke® devices were charged with formulation and allowed to rest for 1 hr before being tested.
- Batch 3: Five Voke® devices were charged with formulation and allowed to rest for 24 hr before being tested.

Apparatus and Procedure

A linear smoking machine was used to extract aerosols from the Voke® devices. Actuation of the devices was enabled using a 67 mL volume, square wave puff profile. Each actuation lasted 1.5 s and puffs were extracted at intervals of 30 s. The puffing regime consisted of a single block of eight puffs that resulted in the extraction of one complete charge from a device (0.45 mg nicotine).

The aerosol generated with each puff, over 8 puffs, was collected in 30 mL of 2,4-dinitrophenylhydrazine (DNPH) derivatization solution. The DNPH aerosol extract solution was allowed to sit for 5 min before continuing with sample preparation. The solution was then filtered via a 0.2 µm nylon microfilter. 0.4 mL of the filtered DNPH aerosol extract solution and 0.6 mL of 0.2% Trizma base solution were transferred to an autosampler vial for analysis using ultra high performance liquid chromatography (UHPLC).

The column used for analysis was Waters Acquity BEH C18 UHPLC column (100 × 2.1 mm; 1.7 µm) with UV detection at 365 nm. Results were obtained using a mobile phase gradient consisting of 300 mL acetonitrile, 620 mL H_2O, 70 mL THF, and 10 mL IPA (A) and 650 mL acetonitrile, 270 mL H_2O, 70 mL THF, and 10 mL IPA (B). The flow rate was set at 0.4 mL/min.

This method was validated for limits of detection (LOD) and limits of quantification (LOQ) as presented in Table 1 in the Supplementary Material. The calculation employed an empirical procedure wherein a half dilution of the lowest standard was analyzed 10 times on separate days; the LOD was calculated as 3 × SD and LOQ was calculated as 10 × SD. The smoking machine was calibrated prior to use; a DNPH solution (30 mL) was spiked with the necessary quantities of carbonyls and assessed as per the method intended for testing Voke (0.4 mL extract in 0.6 mL Trizma base solution).

To determine the effectiveness of the smoking procedure for Voke devices in particular, it was established that the weight of formulation emitted across 8 puffs from a device should be at least 0.7 g (i.e., one charge emitted).
Sample analysis comprised of the following steps:

1. Calibration standard was run as a system check with a separation of each analyte with no valley to be >10%
2. Standards were run. Calibration curves were checked for linearity (correlation coefficient (R^2) > 0.99)
3. Samples were analyzed

A calibration check standard was typically analyzed after every puff block. The calculated values for the check standards were to be within 15% of its nominal value.

Calculations

The results were per block of puffs, i.e., µg/8 puffs. Any carbonyls found in the blank were subtracted from the measured amounts in samples:

$$[\mu_g/\text{block}] = \frac{[\mu g/\text{mL}] \times \text{DNPH vol(mL)} \times (\text{aliquot} + \text{buffer vol})}{\text{Aliquot vol(mL)}}$$

Results were recorded to the nearest 0.01 µg.

Results

No carbonyls were detected in 13 of the 15 samples tested. Acetaldehyde was detected in 2 samples, one tested immediately after charging and the other tested 1 hr after sampling; however, both samples contained the analyte in quantities below its LOQ (3.18 µg/mL). Results obtained have been presented in Table 1 in the Supplementary Material.

Discussion

There has been an increasing interest in the composition of e-liquids and e-cigarette vapors since the detection of carbonyls (such as formaldehyde and acetaldehyde), heavy metals, and tobacco specific nitrosamines in these products.[6,7,13] The

Table 1. Results [ND = Not Detected; LOD-Limit of Detection; LOQ = Limit of Quantification]

		Formaldehyde	Acetaldehyde	Acetone	Acrolein	Propionaldehyde	Crotonaldehyde	MEK (Butanone)	Butyraldehyde
LOD (µg/puff block)		0.36	0.96	1.66	0.91	0.40	0.19	0.75	0.73
LOQ (µg/puff block)		1.22	3.18	5.58	3.05	1.35	0.67	2.53	2.45
Charge time	**Rep**				**Carbonyls puffs 1 to 8 µg/8 puffs**				
Initial	**1**	ND	ND	ND	ND	ND	ND	ND	ND
	2	ND	ND	ND	ND	ND	ND	ND	ND
	3	ND	<3.18	ND	ND	ND	ND	ND	ND
	4	ND	ND	ND	ND	ND	ND	ND	ND
	5	ND	ND	ND	ND	ND	ND	ND	ND
Charge time	**Rep**				**Carbonyls puffs 1 to 8 µg/8 puffs**				
24 hr	**1**	ND	ND	ND	ND	ND	ND	ND	ND
	2	ND	ND	ND	ND	ND	ND	ND	ND
	3	ND	ND	ND	ND	ND	ND	ND	ND
	4	ND	ND	ND	ND	ND	ND	ND	ND
	5	ND	ND	ND	ND	ND	ND	ND	ND
Charge time	**Rep**				**Carbonyls puffs 1 to 8 µg/8 puffs**				
1 hr	**1**	ND	ND	ND	ND	ND	ND	ND	ND
	2	ND	ND	ND	ND	ND	ND	ND	ND
	3	ND	ND	ND	ND	ND	ND	ND	ND
	4	ND	ND	ND	ND	ND	ND	ND	ND
	5	ND	<3.18	ND	ND	ND	ND	ND	ND

mechanism involved in their generation is thought to be the thermal degradation of e-liquid excipients, particularly of propylene glycol and glycerol, the most popular solvents used.[14] E-cigarettes function by heating their e-liquids to vaporization using a resistive metal heater (usually a nickel chromium alloy), with typical maximum temperatures being 180–220°C.[15] Studies have been carried out to examine the effects of temperature (up to 101°C), presence of metals, and aeration/deaeration on the degradation profile of propylene glycol. Lactate, formate, and acetate anions have been noted as its degradation products, whose concentrations were found to increase with increase in temperature and in the presence of a metal under aerated conditions.[16] Additionally, glycerol degradation studies at elevated temperatures have indicated the production of acetaldehyde, acrolein, allyl alcohol, and some unidentified products.[17] It is also hypothesized that formaldehyde generated as a degradation product reacts with propylene glycol and glycerol during vaporization to produce hemiacetals (also known as formaldehyde releasing agents).[9] Further studies on the production of carbonyls and their mechanisms of formation in e-cigarettes are warranted.

The Voke® Inhaler does not involve any heating. It functions by flash atomization of a propellant based solution formulation to generate an aerosol that has been found suitable for pulmonary deposition. Such a mechanism eliminates the possibility of thermal degradation of the formulation excipients. However, the device uses polyoxymethylene (POM) material for some of its components. POM has been reported to have the potential to produce formaldehyde by a variety of mechanisms that includes heat, acids, alkalis, oxygen, abrasion, enzymes, and radiation.[18] There is therefore a theoretical possibility of leaching of carbonyls, such as formaldehyde, from the plastic components of the Voke device when in contact with the formulation. This potential been assessed directly in this study with the result that no carbonyls were detected in 13 of the 15 samples tested, with the other two being below the LOQ. This is in contrast to the results previously reported for e-cigarettes. The absence of heating in the Voke® device offers a significant advantage of not causing thermal degradation of various formulation excipients and thereby providing a safer alternative to smoking.

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Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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