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Determination of Nicotine, Glycerol, Propylene Glycol and Water in Electronic Cigarette Fluids Using Quantitative ^1H NMR

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Abstract

The variability of the electronic cigarette liquids (e-liquid) composition has the potential to influence not only the amount of nicotine delivered to the user, but also the type and amount of generated byproducts and subsequent health risks. For this reason, it is important to characterize all of the chemical components of e-liquids. We report the development and application of a single ^1H NMR analysis method to identify and quantify the most abundant chemical components (nicotine, glycerol, 1,2-propylene glycol, and water) likely to be present as their influence on the composition of inhaled vapor is not known. For ^1H NMR, the solvent has to dissolve the e-liquids at a concentration sufficient to readily determine the concentration of nicotine present, and the solvent and internal standard cannot possess exchangeable protons which would interfere with determining the concentrations of the analytes of interest. To fulfill these requirements, perdeuterated *N,N*-dimethylformamide ($\text{DMF-}d_7$) was selected as the solvent, with 1,2,4,5-tetrachloro-3-nitrobenzene as the internal standard. Nicotine concentrations from 58 different e-liquids obtained using ^1H NMR were found to agree with the results from GC-MS analysis. Generally, the amount of nicotine present was close to that claimed by the manufacturer. In some cases, the proportions of 1,2-propylene glycol, glycerol, and water varied significantly between flavors within a brand and within flavors depending on the nicotine content. In one case, 1,2-propylene glycol was identified where the manufacturer had stated none should be present.

Graphical abstract

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Supplementary Material

Additional supporting information may be found in the online version of this article at the publisher's website.

E-liquids containing nicotine, propylene glycol, glycerol, and water from electronic cigarettes are quantitatively analyzed by a single ^1H NMR analysis.

Keywords

NMR; ^1H ; electronic cigarette; electronic nicotine delivery system; e-liquid; nicotine; glycerol; 1,2-propylene glycol; water

Introduction

Electronic cigarettes (e-cigarettes) or electronic nicotine delivery systems allow the user to inhale nicotine without burning or heating tobacco and their use has been described as safer than tobacco cigarettes and as a means to smoking cessation.^[1-4] As e-cigarettes are currently unregulated in the U.S.A, studies have been undertaken to determine whether their use poses any potential health hazards. The fluid (e-liquid) contained within e-cigarettes has been described as containing less than 10 wt% water and 50-99 wt% organic solvent.^[5] The manufacturer's labels indicate that they contain water with the organic solvent being 1,2-propylene glycol (PG), and/or vegetable glycerol (VG), referred to here as glycerol as its origin was not verified. The e-liquids usually contain nicotine and flavorings, too. However, the actual chemical composition and amounts of these components vary considerably in individual e-liquids. These factors can play an important role in potential toxic and carcinogenic exposures from e-cigarette use.^[6-8] For example, e-liquids are corrosive to the metal components of the e-cigarette devices and may lead to inhalation of high levels of tin, lead and nickel.^[9] Being able to quantitatively determine the composition of the primary carrier solution of an e-liquid is an important aspect for understanding the potential health implications of their use. Because of nicotine's addictive properties, quantifying its concentration is important for determining the addiction potential of an e-liquid. However, published data indicates that manufacturer's labeling of e-liquid nicotine content does not necessarily agree with the independently measured nicotine content.^[10]

Reported analytical methods for e-liquids are predominately based on gas chromatography (GC) and HPLC quantification techniques.^[11] However, none of the reported methods has been used to simultaneously determine the amount of water, PG, glycerol and nicotine that may be present in e-liquids in a single analysis.

The use of ^1H NMR for the quantitative analysis of e-cigarette chemical components has been reported in a few cases with quantification achieved by comparison to an external calibration curve.^[12-14] None of these methods included the use of an internal standard in the NMR sample for quantification. Each of these used a solvent (D_2O , $\text{DMSO}-d_6$) in which hydrogen/deuterium exchange can occur, making these solvents unsuitable for determining the amount of water present in the e-liquid. When water was measured, a separate analysis, Karl Fischer coulometric titration, was used.^[14]

As part of our ongoing investigations into the chemicals contained in e-liquids, we considered ^1H NMR as a single analytical method to identify and quantify the most abundant components, PG, glycerol, water, and nicotine. These chemicals were selected

because variation in the relative proportions of these components may influence the amount of nicotine, flavorings and the type or amount of byproducts inhaled by the user during vaping. In pursuing ^1H NMR, proper selection of the solvent was critical. Not only did the solvent have to dissolve the e-liquids at a concentration sufficient to readily determine the relatively low concentration of nicotine present in the e-liquid (~ 2.4 mg/mL), but it could not possess exchangeable protons, which would interfere with determining the amount of water present. Additionally, the residual ^1H solvent signals could not interfere with those of the e-liquid components. To fulfill these requirements, perdeuterated *N,N*-dimethylformamide ($\text{DMF-}d_7$) was selected as the solvent. We also selected to use an internal standard, 1,2,4,5-tetrachloro-3-nitrobenzene, to support our quantitation efforts. This solvent and internal standard combination was tested first against a surrogate e-liquid (prepared from HPLC water and/or laboratory-grade PG, glycerol, and nicotine) and then applied to e-liquids removed from non-refillable, retail e-cigarette cartridges as well as those available for refillable e-cigarette cartridges.

Results

^1H NMR analysis of the e-liquid surrogates containing PG, glycerol, water, and nicotine demonstrated the ability of the technique to provide reliable quantitative results to within $\pm 8\%$ of the expected values (see Table S-3 Supplementary Material). The technique was then applied to the analysis of e-liquids from blu eCigs[®] and V2[®] e-cigarette cartridges as well as iVape e-liquid refill solutions.

Table 1 lists the results from ^1H NMR analysis of two e-liquids, each with four different concentrations of nicotine. Results from the analysis of an additional 10 e-liquids extracted from these same e-cigarette brands, each with four different concentrations of nicotine, are provided in the Supplementary Material. Table 2 lists the results from ^1H NMR analysis of two e-liquid refill solutions, each with five different concentrations of nicotine.

Figure 1 shows the 3.2 to 4.8 ppm portion of a representative ^1H NMR spectrum of an e-liquid containing each of the four components. PG (1.1, 3.4, and 3.7 ppm), glycerol (3.5 and 3.6 ppm), and water (3.9 ppm) are readily identified and signal overlap only occurs with the hydroxyl protons (4.6–4.7 ppm) of PG and glycerol; the water peak is independent of these. The hydroxyl protons of PG and glycerol were not used in calculating the amounts present, but their integrals were generally found to be within $\pm 10\%$ of theoretical relative to the methyl, methylene, and methine protons of PG and glycerol.

Because no exchange of hydroxyl protons of PG and glycerol (4.64 and 4.70 ppm) occurs in $\text{DMF-}d_7$, they contribute to the splitting of protons on the adjacent carbons. The methine proton of glycerol appears as a multiplet representing a doublet of the ABXA'B' splitting pattern (3.64 ppm, $J_{\text{CH-CH}_2}$ 5.4 Hz, $J_{\text{CH-OH}}$ 4.7 Hz), while the multiplets for each methylene proton result from a further splitting of the ABX pattern (ddd, 3.50 and 3.54 ppm, $J_{\text{CH}_2\text{-OH}}$ 5.7 Hz). The protons attached to the carbons of PG represent an XABM3 pattern, from which the XAB protons are further split by the hydroxyl proton. The methyl protons of PG are a doublet (1.09 ppm, $J_{\text{CH}_3\text{-CH}}$ 6.3 Hz), the methine proton multiplet results from overlapping dddq (3.74 ppm, $J_{\text{CH-OH}}$ 4.4 Hz) and each methylene proton is an overlapping

ddd (3.35 and 3.41 ppm, $J_{\text{CH}_2\text{-CH}}$ 5.4 Hz, $J_{\text{CH}_2\text{-OH}}$ 5.7 Hz). The water signal occurs as a singlet at 3.91 ppm.

Figure 2 shows the 7.2 to 9.0 ppm portion of the same e-liquid ^1H NMR spectrum. The aromatic hydrogens of nicotine are observed in this region along with the internal standard and residual ^1H from DMF- d_7 . The signals of the alkyl ^1H of nicotine ($\text{H}_2', \text{H}_3', \text{H}_4', \text{H}_5', \text{H}_6'$) are observed in the 1.5 to 3.2 ppm region (Figure 1).^[15] While other signals from the e-liquids appear in this region, two to four distinct nicotine signals are observed; the specific ones depend on what other components are present. Residual DMF methyl- ^1H signals also appear in this region.

Discussion

^1H NMR analysis was found to be a convenient and reliable multi-analyte method for quantifying the amounts of PG, glycerol, water, and nicotine in the 58 different e-liquid nicotine/flavor combinations. The amount of nicotine determined using ^1H NMR compared well with that obtained using GC-MS. As shown, the composition of the e-liquids, with respect to PG, glycerol, and water, varied by more than 10% within a brand and even within a flavor, depending on nicotine content.

As described by the manufacturer, the e-liquid in V2[®] cartridges contained PG and VG. The amount of PG in all of these e-liquids ranged from 608 to 797 mg/mL, while the amount of glycerol ranged from 152 to 369 mg/mL. The amount of water in all of these e-liquids also had a wide concentration span, ranging from 56.2 to 201 mg/mL. The PG and VG used to formulate these may not have been anhydrous and may be the source of water in those with very low water concentrations. Within a given V2[®] flavor, the amounts of PG, glycerol and water often were found to differ significantly depending on the amount of nicotine present. The greatest difference for the amount of PG was 78 mg/mL (Sahara with nicotine at 0 and 6 mg/mL). The Sahara flavor also had the greatest difference for glycerol (51 mg/mL). The Green Tea Menthol flavors with 6 and 24 mg/mL of nicotine had the greatest difference in water concentration (145 mg/mL).

The blu eCigs[®] cartridges tested are described by the manufacturer as containing only VG, water, nicotine and flavorings. However, Java Jolt 0 was found to contain 67.8 mg/mL of PG. The amount of glycerol in all of the blu eCigs[®] e-liquids analyzed ranged from 753 to 1048 mg/mL, and the amount of water ranged from 124 to 303 mg/mL. Within a given flavor, the greatest difference in the amount of glycerol was 214 mg/mL (Java Jolt, 0 and 16 mg/mL of nicotine), while the greatest difference in water concentration was 75 mg/mL (Piña Colada, 0 and 6-8 mg/mL of nicotine).

In most cases, the amount of nicotine determined by ^1H NMR and GC-MS was about the same or less than that claimed by the manufacturer (Table 1 and Table S-2 Supplementary Material). For example, the averaged amount of nicotine by ^1H NMR and GC-MS analyses of V2[®] Menthol 6 is 16% less than that claimed by the manufacturer and the averaged amount of nicotine in blu eCigs[®] Magnificent Menthol 16 is 25% less than claimed.

¹H NMR and GC-MS each provided reliable quantitation of nicotine based on the 10% relative standard deviation (RSD) across five replicates for each method, except when a very low concentration of nicotine was detected by GC-MS in one of the replicates where no nicotine was expected (Java Jolt 0, Vivid Vanilla 0, Sahara 0; see Table S-2 Supplementary Material). The amount of nicotine determined by ¹H NMR compared well to that obtained by GC-MS, generally differing by <15%, except for two notable differences: blu eCigs® Java Jolt medium (24 % RSD) and Piña Colada 6-8 (33 % RSD). The GC/MS nicotine determination was greater for the Java Jolt flavor, while the ¹H NMR-determined nicotine concentration was greater for the Piña Colada flavor. In both cases there was <2.50 mg/mL difference between the average nicotine levels determined by each method.

The amount of glycerol, water, and nicotine in blu eCigs® Cherry Crush 16 e-liquid has been reported previously as 77%, 14%, and 2%, respectively, though the method of calculation (e.g., wt/wt%) was not provided.^[16] We found 901 mg/mL of glycerol, 136 mg/mL of water, and 14.1 mg/mL of nicotine (¹H NMR). Based on the measured density of 1.17 g/mL, our values correspond to 77, 12, and 1.2 wt/wt%, respectively, indicating good agreement with the previous report.

The amounts of PG and VG in the iVape e-liquids are claimed to be approximately 60% and 40%, respectively.^[17] The NMR data showed the amount of PG in these e-liquids ranged from 436 to 727 mg/mL, while the glycerol ranged from 322 to 667 mg/mL (Table 2). The variability of PG and glycerol were greater in the Carolina Crush flavor than in the HyperMint flavor. Water was a minor component, ranging from 5.19 mg/mL (Carolina Crush 18) to 119 mg/mL (HyperMint 24) though most had about 10 to 30 mg/mL. The PG and glycerol used to formulate these may not have been anhydrous and may be the source of water instead of it being intentionally added. In most cases, the amount of nicotine determined by ¹H NMR was about the same as that claimed by the manufacturer. Only HyperMint 6 and Carolina Crush 6 contained nicotine at amounts that differed from the manufacturer's claim by more than 10%.

To the best of our knowledge, this is the first study to report a single quantitative analysis of the four most abundant components of e-liquids. Through ¹H NMR analysis of laboratory-prepared mixtures and the comparison of results for nicotine in e-liquids with those from GC-MS, a robust method to reliably and accurately determine each of these components simultaneously has been demonstrated.

Experimental Section

The e-liquid was obtained from individual blu eCigs® or V2® e-cigarette cartridges by removing the wicking material containing the e-liquid and compressing it in a disposable syringe to expel the liquid into a small glass vial with a PTFE-lined screw cap. The wicking material is a gauze-like material used to absorb the e-liquid within the e-cigarette cartridge. Approximately 0.3-0.5 mL of liquid was obtained from each cartridge. Each refill solution was shaken well before removing an aliquot for analysis.

LOD and LOQ for each analyte were determined using the standard deviation and slope from calibration curves in which a low standard, prepared from laboratory chemicals, is approximately 10-30 times the anticipated LOD (see Table S-1). The S/N of the NMR signals from the low standard then was used to check the calculated LOD. Because of the possible interference of one component with another, the LOD and LOQ for glycerol were determined by adding known quantities of glycerol to 100 μ L of PG, and those for PG were determined by adding PG to 100 μ L of glycerol. The calculated LOD and LOQ for glycerol in PG are 0.096 mg/mL and 0.29 mg/mL, respectively. The calculated LOD is less than that based on the S/N of the methine proton. For PG in glycerol, the calculated LOD and LOQ are 0.081 mg/mL and 0.25 mg/mL, respectively. However, analysis of a standard at 1.4 times the concentration of the calculated LOQ showed that only the methyl protons were observable with the others coincidental with the glycerol signals. Based on the S/N for the methine proton in the low standard, the LOD and LOQ for PG are estimated to be 0.38 mg/mL and 1.3 mg/mL, respectively. The LOD and LOQ for nicotine and water were determined by adding known quantities of each to a 75:25 mixture of PG and glycerol, which is typical for the e-liquids. The calculated LOD and LOQ for nicotine are 0.16 mg/mL and 0.49 mg/mL, respectively. However, the S/N for one of the methylene protons of the pyrrolidine moiety (H4'a) of the low nicotine standard is only 3.7 indicating the LOD is 1.3 mg/mL. The LOD and LOQ for water are 0.017 mg/mL and 0.052 mg/mL. The amount of water present in the DMF-*d*₇ used for all samples and standards ranged from 0.31 to 2.4 mg/mL and results were corrected by the amount found in the blanks analyzed with each batch of samples.

NMR Spectroscopy

An aliquot (50 or 100 μ L) of each well-mixed e-liquid was dissolved in DMF-*d*₇ (550 or 500 μ L) containing 30 mg/mL of 1,2,4,5-tetrachloro-3-nitrobenzene as an internal standard. The ¹H NMR spectra were obtained using a Bruker Advance 500 NMR operating at 500.133 MHz with a 5-mm broad band inverse (BBI) probe at 298 K, a 90° pulse width of 7.0 μ s, and decoupled to ¹³C. Sixty-four scans, each with a 60 s relaxation time, were collected. The amount of each component was determined by using the resulting weighted average of integrals for the relevant protons. For glycerol and PG, all protons bound to carbon were used. For nicotine, H4 and a subset of H2', H3', H4' and H5' were used. Fewer scans could be used if not measuring nicotine.

GC-MS

GC-MS analyses were performed using an Agilent 6890 GC coupled to an Agilent 5973 MSD. For GC-MS analysis of nicotine, 25 μ L of e-liquid was diluted to 10 mL with acetonitrile. Analyses were performed using a DB-5MS column (60 m, 0.32 μ m diameter with 0.25 μ m film) by injection of 1 μ L into a 290 °C splitless inlet. The GC oven was held at 100 °C for 3 min, ramping at 10° C/min to 150 °C, then 6 °C/min to 290 °C and held for 8.67 min. The MS was scanned 35 to 500 amu with a 6.80 min solvent delay. Quantitation for nicotine was determined by comparison of the instrument response with that from an 8-point calibration curve (1.25, 2.5, 5.0, 10, 30, 50, 75, 100 μ g/mL) with naphthalene-*d*₈ as the internal standard. The quantitation ion for nicotine was m/z 84 with m/z 163, 162, and 133

as confirmation ions. The quantitation ion for naphthalene-*d*₈ was *m/z* 136 with *m/z* 108 as the confirmation ion. The LOD and LOQ for nicotine determined by GC-MS analysis are 0.149 ng/mL and 0.452 ng/mL, respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Portion (3.2-4.8 ppm) of ^1H NMR in $\text{DMF-}d_7$ for V2[®] Menthol 12 electronic cigarette liquid which contains PG, glycerol, water, nicotine and internal standard. Signals for nicotine and the internal standard do not occur in the 3.4 to 4.0 ppm range.

Figure 2. Portion (7.0-9.0 ppm) of ^1H NMR in $\text{DMF-}d_7$ for V2[®] Menthol 12 e-liquid which contains PG, glycerol, water, nicotine and internal standard showing the aromatic- ^1H signals of nicotine (7.42 (H5), 7.82 (H4), 8.52 (H6) and 8.56 (H2) ppm) and those of the IS (8.39) and residual ^1H of $\text{DMF-}d_7$ (8.02 ppm).

Table 1Results from ^1H NMR and GC-MS Analysis of E-Liquids from E-Cigarette Cartridges ($n = 5$)

Brand and Flavor	Nicotine, mg/mL (%RSD)			PG, Glycerol and Water, mg/mL (%RSD) from NMR Analysis		
	Claim by manufacturer	GC-MS	NMR	PG	Glycerol	Water
V2 [®] Menthol	0	<LOD *	<LOD	672 (3.3)	354 (3.3)	66.8 (3.1)
	6	4.98 (2.7)	5.03 (5.7)	669 (2.8)	369 (2.8)	66.4 (4.7)
	12	8.93 (6.7)	8.98 (2.5)	608 (1.8)	328 (1.8)	125 (1.3)
	24	19.3 (7.8)	19.9 (2.0)	617 (2.2)	329 (2.0)	81.1 (1.9)
blu eCigs [®] Magnificent Menthol	0	<LOD	<LOD	<LOD	970 (5.8)	217 (6.5)
	6-8	5.93 (1.5)	5.33 (8.0)	<LOD	982 (1.6)	207 (1.3)
	12	9.41 (5.8)	9.55 (3.9)	<LOD	992 (3.6)	207 (4.6)
	16	12.2 (6.7)	11.6 (4.3)	<LOD	910 (3.8)	170 (8.1)

* <LOD = less than the limit of detection; see the Experimental section in the Supplementary Material for further details.

Table 2¹H NMR Analysis Results from E-Liquid Refill Solutions, mg/mL, n= 3 (%RSD)

Brand and Flavor	Nicotine claimed by manufacturer, mg/mL	Components from NMR Analysis, mg/mL (%RSD)			
		Nicotine	PG	Glycerol	Water
iVape HyperMint	0	<LOD *	549 (1.7)	471 (1.7)	11.6 (3.4)
	6	5.13 (4.8)	571 (4.0)	420 (4.7)	10.3 (14)
	12	11.8 (4.1)	489 (4.0)	504 (4.1)	29.4 (0.97)
	18	19.3 (0.94)	529 (2.9)	527 (2.6)	11.1 (14)
	24	21.8 (4.0)	469 (4.0)	448 (3.8)	119 (3.7)
iVape Carolina Crush	0	<LOD	621 (4.1)	408 (5.3)	30.6 (4.4)
	6	6.98 (12)	436 (6.4)	667 (6.4)	21.5 (3.4)
	12	12.3 (6.5)	727 (0.73)	322 (0.84)	19.8 (15)
	18	19.3 (4.5)	544 (3.7)	493 (4.1)	5.19 (15)
	24	23.0 (3.4)	590 (3.9)	435 (3.6)	21.8 (4.2)

* <LOD = less than the limit of detection; see the Experimental section in the Supplementary Material for further details.