Review Article

Chromatography and Spectroscopy Methods for the Analysis of Nicotine and Other Chemical Ingredients in E-Liquid Formulation: A Review

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ABSTRACT

Spectroscopy and chromatography methods have become the most preferred techniques for detecting ingredients in e-liquid analysis. Both methods are widely used for separating and quantifying volatile compounds in a sample, providing individual chemical information in complex mixtures. This paper aims to review the detection and quantification of nicotine and other chemical ingredients in e-liquid used in e-cigarettes. E-cigarettes use the evaporation-condensation principle of aerosolization to produce an inhaled vapor containing nicotine, excipients, and flavoring agents. This review covers sample preparation, identification, and quantification of nicotine and other ingredients using chromatography and spectroscopy analysis. The spectroscopy methods are useful for quickly identifying and quantifying volatile compounds, including propylene glycol (PG), vegetable glycol (VG), and nicotine, while spectroscopic methods, particularly the Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR) method, have lower analytical performance compared to chromatography methods in detecting nicotine and other chemical ingredients. Based on the review, chromatographic methods are the primary option for analyzing nicotine in all e-liquid samples, offering a better alternative for a future study with the presence of multiple detectors.

Keywords: Aerosolization, chromatography, e-cigarettes, e-liquid, ingredients, nicotine, quantification, spectroscopy

INTRODUCTION

Nicotine is an organic compound that belongs to the pyridine alkaloids. According to IUPAC nomenclature, nicotine is known as 3-(1-methyl-2-pyrrolidinyl) pyridine, with the chemical formula $C_{10}H_{14}N_2$. Nicotine is a naturally produced dinitrogen alkaloid present in dried leaves of Solanaceae, specifically the tobacco plant, with concentrations as high as 3% (*Nicotiana tabacum*) (Kimbrough, 2019). The molecular structure of nicotine and other common materials in e-liquid are shown in Figure 1.

Nicotine exists in a variety of forms, including freebase, non-protonated Form 1, and protonated Forms 2 and 3 in solution. Typically, nicotine appears as a colorless or pale-yellow liquid that is very hygroscopic and oily, with an uncomfortable strong odor. It is the main addictive component in tobacco products and e-liquids.
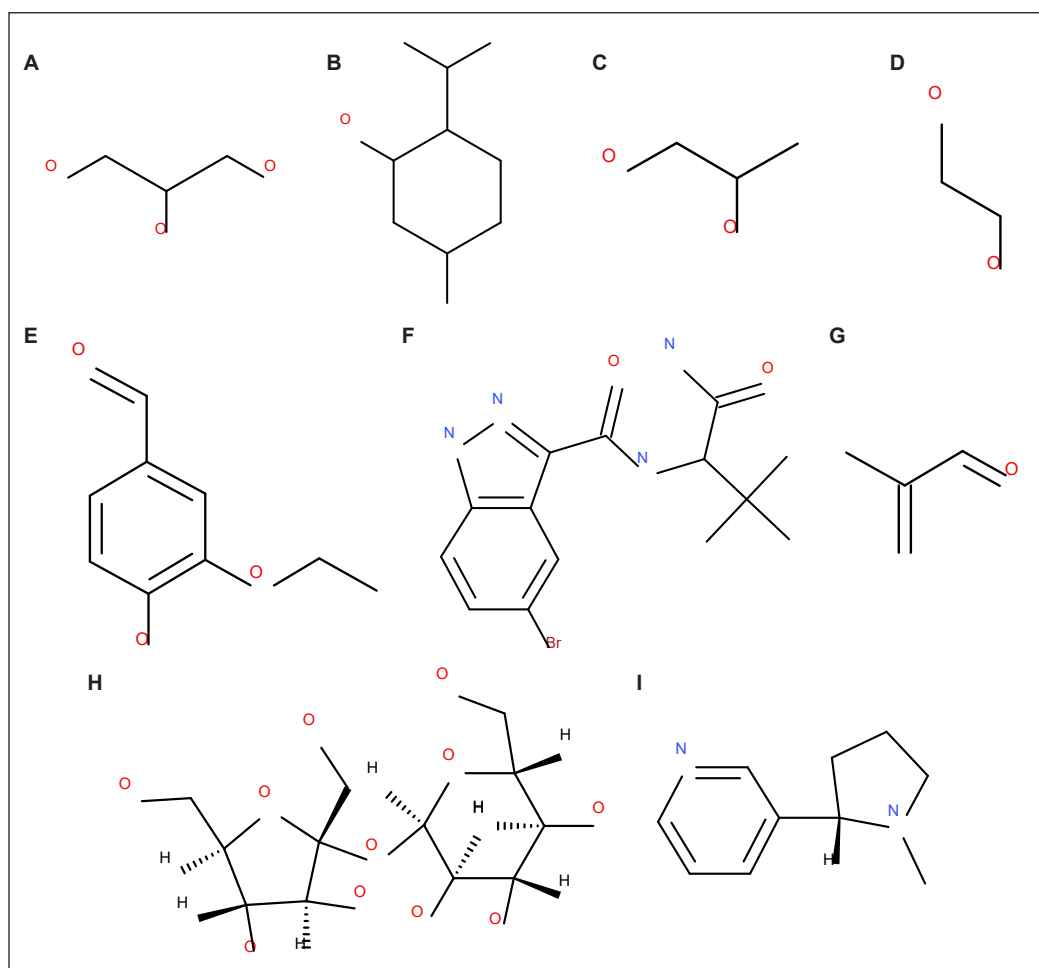

Figure 1. Molecular structure: (A) Glycerol; (B) Menthol; (C) Propylene glycol; (D) Ethylene glycol; (E) Ethyl vanillin; (F) N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-5-bromo-1H-indazole-3-carboxamide (ADB-BRINACA); (G) methacrylaldehyde; (H) sucrose; and (I) nicotine

E-liquids in electronic cigarettes (e-cigarettes) come in various packaging types and formulations. Generally, the main ingredients found in e-liquid formulations are vegetable glycerin, propylene glycol, flavoring liquids, as well as nicotine (Cao et al., 2021; Heldt et al., 2021). With the new generation of e-cigarettes, users can customize e-liquids based on their preferences (Vivarelli et al., 2022). Keeping up with the new generation of e-liquid formulations is a significant challenge for analysts because nicotine may be difficult to identify and detect. Moreover, the use of prohibited chemicals in e-liquid formulations raises significant concerns for consumers because currently, there are no restrictions or laws for users to customize their e-liquids, and electronic cigarettes and their e-liquid formulations are virtually unregulated in some countries (Giroud et al., 2015).

Nicotine is a central nervous system (CNS) stimulant that increases alertness and can reduce appetite. Consumption of nicotine can result in different sensations compared to other drugs like amphetamines, heroin, cocaine, and crack, as the main symptoms may include dizziness, nausea, or vomiting. Although the harmful effects of nicotine may not be immediately observable, nicotine and additives are toxic chemicals that should be controlled and monitored, as they are classified as reproductive or developmental toxicants (RDT) and addictive (AD) (Patel et al., 2021).

Table 1 compares the legislative status of nicotine in e-liquids between Southeast Asia and other countries. The Nicotine Concentration in Vaping Products Regulations is a Canadian regulation that sets maximum nicotine concentration limits for vaping products sold in Canada (Canada.ca, 2021). According to this regulation, the maximum allowable nicotine concentration for vaping products sold in Canada is 20 mg/ml, irrespective of whether they are locally produced or imported. UAE.S Standard (2019) is a standard for electronic cigarettes and e-liquids issued by the Emirates Authority for Standardization and Metrology (ESMA) in the United Arab Emirates (UAE). The nicotine content in the electronic liquid must be less than or equal to 20 mg/ml as regulated by this standard. In New Zealand, under the Smokefree Environments and Regulated Products (Vaping) Amendment Act 2020, the maximum allowable nicotine concentration in e-liquids is also

Table 1

Legislation of nicotine concentration level in e-liquids in different countries

Country	*(mg/ml)	Reference
Canada	less than 20	Canada.ca, 2021
Saudi Arabia	less or equal to 20	UAE.S Standard, 2019
New Zealand	less than 20	New Zealand Legislation, 2020
Philippines	NA	NA
Singapore	NA	NA
Malaysia	NA	NA

*Maximum nicotine concentration level in e-liquid. NA indicates not available

20 mg/ml. Therefore, any e-liquid sold or supplied in New Zealand must not contain more than 20 mg of nicotine per milliliter of liquid.

The sale, importation, and distribution of e-liquids containing nicotine are prohibited in Singapore, the Philippines, and Malaysia until March 2023, resulting in the absence of regulated nicotine concentrations in e-liquids. It is important to note that the regulation of e-cigarettes and vaping products in Southeast Asian countries is still evolving, and there may be updates to the guidelines in the future. Therefore, individuals and businesses involved in the vaping industry are advised to stay updated on the latest regulations and guidelines from their respective countries' authorities.

In Malaysia, nicotine is only covered by the main law, the Malaysian Poison Act 1952. Only authorized persons, such as registered doctors and pharmacists, can handle nicotine and nicotine-containing products. However, nicotine in tobacco is exempted from this classification. To fully address the issue of legalizing e-liquid in Malaysia, it is essential to go beyond simply excluding e-liquid from the Poisons Act 1952. Proper regulation is also needed to ensure that sales are restricted to those over 18, sales and marketing are properly regulated, and the ingredients are closely monitored.

After April 2023, e-liquid is legal, but there are no regulations on the ingredients and prohibited compounds in Malaysia. Implementing regulations is crucial to controlling nicotine concentration and hazardous flavorings containing diacetyl. Failure to do so could result in unsafe nicotine concentration levels, as demonstrated by the 20mg/ml limit enforced in Canada, Saudi Arabia, and New Zealand. A flat tax rate per ml should be established to avoid the difficulties associated with determining nicotine concentration for taxation purposes. It would discourage misdeclaration and ensure a fair and easy taxation system.

Gas chromatography (GC) and liquid chromatography (LC) have been commonly used for determining nicotine levels in e-liquids in the presence of different detectors. However, new methods have also been proposed, including spectroscopic techniques like nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, and Raman spectroscopy. While GC has traditionally been the preferred method, the spectroscopy techniques offer numerous advantages as a qualitative method.

The recommended method of ISO 20714 (2019) for determining nicotine in e-liquids, according to the International Organization for Standardization (ISO), is classified as a quantitative method.

This review aims to identify and quantify the presence of nicotine in commercially available e-liquid formulations used in e-cigarettes using several analytical methods. Consequently, determining the nicotine concentration may contribute to establishing any requirements regarding national regulations.

METHODOLOGY

Scientific articles were identified and selected from several sites such as ScienceDirect andPubMed until December 2022 using the keywords: "e-cigarette," "electronic cigarette device," "vape," "e-liquids," "toxic compounds," "nicotine," "toxic," "quantification," "identification," "chromatography," and "spectroscopy." A total of 31 references were used, including papers related to the scientific research with specific criteria set up to decide each paper. The criteria required must be (1) an original science-related research article, (2) an original science-related review article, or (3) related to the subject of chemistry. All the scientific articles were carefully chosen to match the main purposes of the review.

RESULTS AND DISCUSSION

Sample Preparation

"E-liquids" are typically sold as viscous liquid solutions in bottles in many countries (Almazrouei et al., 2022; Augustini et al., 2021; Ketonen & Malik, 2020; Laestadius et al., 2019; Patel et al., 2021). They come in a variety of complex formulations that include a mixture of hundreds of volatile and non-volatile compounds (Eddingsaas et al., 2018; Li et al., 2021; Patel et al., 2021). They also come in two types: flavored e-liquids and non-flavored e-liquids (Augustini et al., 2021). Prior to chromatography analysis, e-liquid samples need to be removed from their respective bottle packaging (Almazrouei et al., 2022). Before gas chromatography analysis, sample preparation, such as adding an internal standard (IS), dissolution, dilution, homogenization, and pre-concentration. Adding an internal standard to the sample is sometimes required for specific purposes, such as data analysis (Patel et al., 2021; Qin et al., 2022). Common GC solvents for the dissolution of e-liquids include methanol, dichloromethane, and hexane. The common sample-to-solvent ratio for dilution is 1:4, 1:9, and 1:10 (Almazrouei et al., 2022; Augustini et al., 2021; Cowan et al., 2022). Recently, an innovative method, such as QUECHERS extraction, has been applied, which can successfully reduce the matrix effect in sample formulations (Almazrouei et al., 2022). These laboratory techniques may result in simple or complicated chromatograms or time-consuming calibrations. The chromatogram will help to understand the formulation of e-liquids, whereas incompatible sample preparation processes could reduce the identification and quantification of nicotine and other ingredients in e-liquids.

Current Analytical Methods for e-liquid Samples

Gas Chromatography-Mass Spectrometry (GC-MS). GC-MS is widely recognized as the gold standard technique for analyzing e-liquids due to its ability to provide highly specific spectral data on individual compounds in a complex mixture while requiring minimal sample separation. When dealing with viscous liquid solutions, sample preparation

typically involves a series of steps, including sample removal, dissolution, extraction, and clean-up. However, the derivatization of the sample is not reported during the GC analysis. Each step in the pre-treatment of the sample before analysis is crucial for enhancing the analytes' recovery and the method's sensitivity. However, as the number of pre-treatment steps increases, the method becomes more complex, and the analysis time also increases.

The analysis of e-liquids has long benefited from the Gas Chromatography (GC) method. GC can provide an easy way to analyze qualitatively and quantitatively, making it a highly advanced method for nicotine analysis. In identifying the volatile compounds in e-liquids, gas chromatography coupled with mass spectrometry (GC-MS) is one of the most widely used analytical methods in understanding the complexity and the mass-to-charge ratio of molecules in the formulations. Gas chromatography with flame-ionization detection (GC-FID) method is rarely used in the study of e-liquids except in the 2018 study, which was used to quantify levels of major components in e-liquids (Dai et al., 2018).

GC characterizes chemical compounds in e-liquids due to their volatile properties. Although e-liquids are a complex formulation, GC can quickly separate many compounds. For example, nicotine was identified after 10 minutes of injection into the GC column and other compounds such as PG and glycerol (Almazrouei et al., 2022). DB-5MS capillary column and HP-5MI Ultra Inert column are frequently used in GC methods to analyze e-liquids (Almazrouei et al., 2022; Cowan et al., 2022). For 2D chromatography, Rxi®-624Sil MS column and Stabilwax® column were used (Patel et al., 2021). These non-polar columns separate many volatile compounds in e-liquids, including nicotine.

The GC-GC-TOF method used headspace analysis to identify an extensive range of toxic compounds in e-liquids of six common flavors obtained online in Australia (Patel et al., 2021). Nicotine was one of the 1064 volatile compounds identified in all tested samples in a 2021 study. Similarly, headspace analysis of blood orange-flavored e-liquids using GC-IMS and GC-MS in Germany and Poland also found nicotine among the 37 volatile compounds identified (Augustini et al., 2021). GC-IMS used a retention index and was validated using GC-MS data. Figure 2 displays an example of an e-liquid sample chromatogram demonstrating the separation of multiple components at different concentration ratios. This particular e-liquid sample contains drugs of abuse, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), alongside nicotine, PG, and glycerol (Almazrouei et al., 2022).

A powerful MS method with chromatographic capability is essential for targeted screening. In a study of 27 e-liquid samples for screening humectant and active ingredients, a Direct Analysis in Real Time™ ionization source coupled to a JEOL JMS-T100LC AccuTOF™ mass spectrometer (JEOL USA, Inc., Peabody, MA) (DART-MS) was used (Peace et al., 2016). For example, the DART-MS spectrum of the Cherry flavor e-liquid sample contains the protonated molecular ion of nicotine, glycol, and several flavor additives within 5 mmu, as shown in Figure 3.

However, several low-intensity peaks that should correspond to components of the formulation were left unidentified using this method. Despite its efficiency, rapidity, and lack of sample preparation requirements, this targeted screening method can be expensive due to the need for reference standards, high temperatures, and a large helium flow rate (2 L/min).
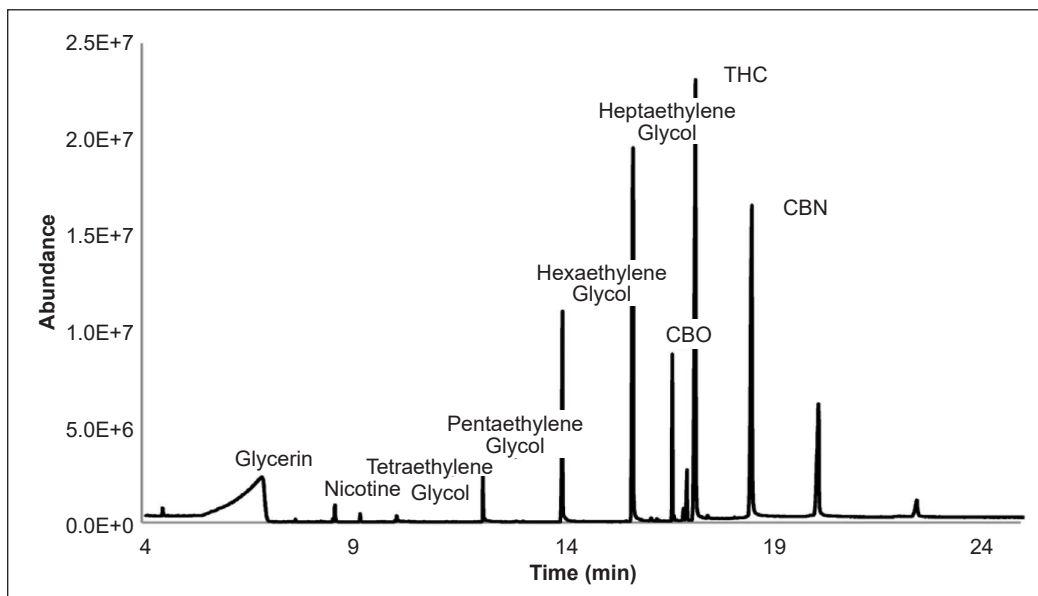

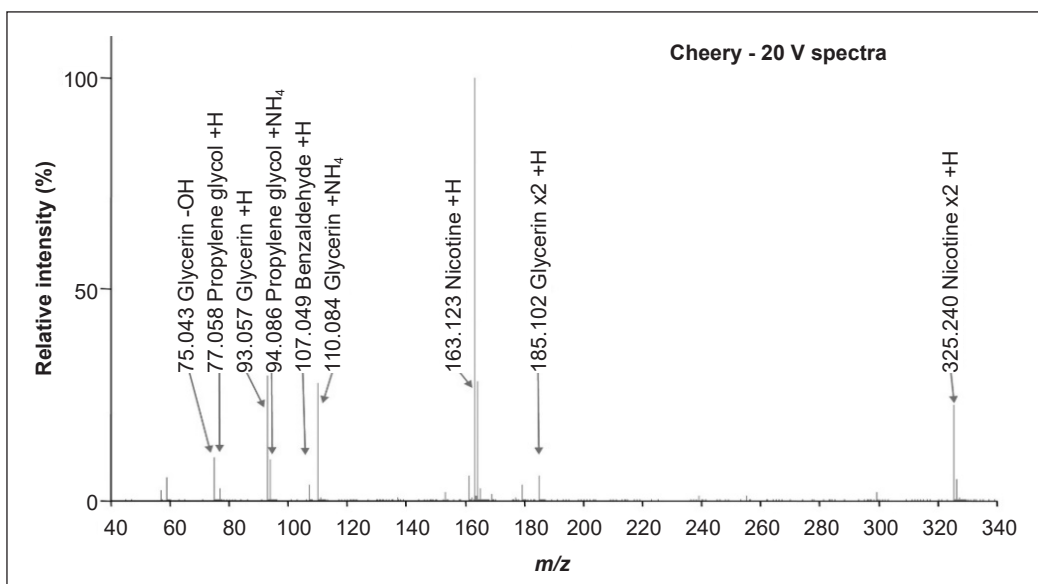*Figure 2.* An example of an e-liquid sample chromatogram by GC-MS (Almazrouei et al., 2022)

Figure 3. DART-MS 20 V spectra of the e-cigarette liquid formulations named Cheery (Peace et al., 2016)

High-Performance Liquid Chromatography (HPLC). The current discussion focuses on the sample preparation, screening, and identification of nicotine in e-liquids using high-performance liquid chromatography (HPLC). The discussion evaluates the capabilities of several liquid chromatography methods coupled with different types of detectors.

In the HPLC method, sample treatment is required before injecting the sample into the chromatographic system. The liquid samples need to be diluted 10,000 fold with ACN:H2O (1:9, v/v) before evaluating the concentration of nicotine (Aszyk et al., 2018). After injecting a 5 µL sample into liquid chromatography-tandem mass spectrometry with electrospray ionization (HPLC-ESI–MS/MS), nicotine and 42 other compounds were detected. In addition to dilution, the samples need to be prepared under acidic and basic conditions before separating the components in the e-liquid samples obtained in Poland (Aszyk et al., 2018).

Since the first detection of nicotine in 2015, the compositions of e-liquid formulations have changed over time. Liquid chromatography coupled to diode-array detection (LC-DA) has proven efficient for detecting nicotine concentrations in various nicotine-labeled and unlabeled e-liquid products (Davis et al., 2015). A single wavelength of detector at 260 nm is typically used for nicotine analysis in e-liquids. Similarly, after undergoing the electromembrane extraction (EME) process, nicotine was detected in aerosol matrices from e-cigarettes at a similar wavelength (259 nm). In contrast, a recent research study 2019 used liquid chromatography coupled to photodiode-array detection (LC-PDA) to detect nicotine and multiple nicotine-related alkaloids (Palazzolo et al., 2019). The average nicotine concentration ranged from 18 to 25 mg/mL, and multiple nicotine-related alkaloids were also detected using LC-PDA. The UV wavelengths of the PDA detector were set between 230 nm and 300 nm to detect multiple nicotine-related alkaloids. In addition to the HPLC-DA and PDA methods, a 3200 Q Trap (Applied Biosystems, Foster City, CA) attached to an SCL HPLC system (Shimadzu, Columbia, MD) high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS-MS) system was used to confirm and quantify nicotine in 27 e-liquids (Peace et al., 2016). HPLC methods have many advantages, including high specificity, high separation of nicotine and other components, and the availability of multiple detectors on the market. However, it is less likely to be chosen as it is only available in well-known university laboratories.

LC-DA proved efficient for detecting nicotine concentration in various nicotine-labeled and unlabeled e-liquid products (Davis et al., 2015). A single wavelength detector at 260 nm is normally utilized in nicotine analysis in e-liquids. On the other hand, nicotine was detected in matrices of aerosols from e-cigarettes at a similar wavelength (259 nm) after undergoing the electromembrane extraction (EME) process. In contrast, a recent research study 2019 used liquid chromatography coupled to photodiode-array detection (LC-PDA) to detect nicotine and multiple nicotine-related alkaloids (Palazzolo et al., 2019). The

average concentration of nicotine was found in a range between 18 to 25 mg/mL. Nicotine combined with multiple nicotine-related alkaloids was also detected using LC-PDA. The UV wavelengths of the PDA detector were set between 230 nm and 300 nm to detect multiple nicotine-related alkaloids.

Besides HPLC-DA and PDA method, a 3200 Q Trap (Applied Biosystems, Foster City, CA) attached to an SCL HPLC system (Shimadzu, Columbia, MD) high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS-MS) system was used for the confirmation and quantitation of nicotine in 27 e-liquids (Peace et al., 2016).

HPLC method has many advantages, including high specificity, high separation of nicotine and other components, and availability of multiple detectors in the market, but it is less likely to be chosen as it is only available in well-known university laboratories.

Nuclear Magnetic Resonance (NMR) Spectroscopy. NMR is one of the spectroscopy methods used to identify nicotine and other compounds, including those not mentioned in the formulation. In the absence of nicotine in the formulation, NMR was applied for the analysis of e-liquids containing synthetic cannabinoids with different types of magnetic strength: high field (HF) and low field (LF) (Wu et al., 2021). HF method is useful compared to LF because the complexity of ^{1}H NMR signals can be enhanced, and using ^{19}F NMR can confirm the presence of fluorine in cannabinoids.

The NMR method can also be implemented to observe e-liquid signals containing nicotine. As seen in Figure 4, the aromatic proton signal of the e-liquids (for instance, from nicotine and ethyl vanillin) can be observed at low field region between δ 6 and 10 ppm, while the mid-field region contains signals associated with solvents such as glycerol, propylene glycol, and ethylene glycol (Hahn et al., 2014). Despite distinctive H signals at the low field region and using a 400 MHz spectrometer, ^{1}H NMR is unsuitable for quantifying nicotine because they showed strong overlap signals with other matrix compounds at the middle to high field region.

Infrared (IR) Spectroscopy. IR spectroscopy has several advantages, including its simplicity, which allows non-spectroscopists to perform the analysis. Additionally, vibrational spectroscopy methods provide rapid analysis, with results obtained within seconds, and it is non-destructive, meaning that it does not require sample preparation or the use of chemical
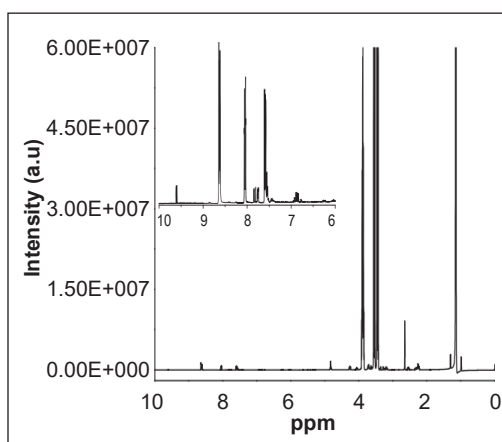

Figure 4. ^{1}H NMR spectrum of the aqueous sample of a typical e-cigarette liquid sample (Hahn et al., 2014)

reagents. Before acquiring the IR spectra, e-liquid samples must be taken out of their plastic containers, as the IR source cannot penetrate the sample in the plastic. In a large study of e-liquid samples (n=68, containing both nicotine and non-nicotine samples), the Infrared spectroscopy (IR) method was used to detect nicotine concentration, which was acquired from Belgium. The study used a Nicolet iS10 FT-IR (ThermoFisher Scientific, Waltham, USA) spectrometer equipped with a Smart iTR accessory and a deuterated triglycine sulfate (DTGS) detector (Deconinck et al., 2016). As seen in Figure 5, Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR) and the Near Infrared Spectroscopy (NIR) method were used to observe the difference between the spectrum of the samples and the spectrum of pure nicotine (reference standard). However, it was impossible to identify their spectral differences. Using a low-resolution (4 cm^{-1}) spectrometer in this experiment hindered the vibrational assignment for several weak IR
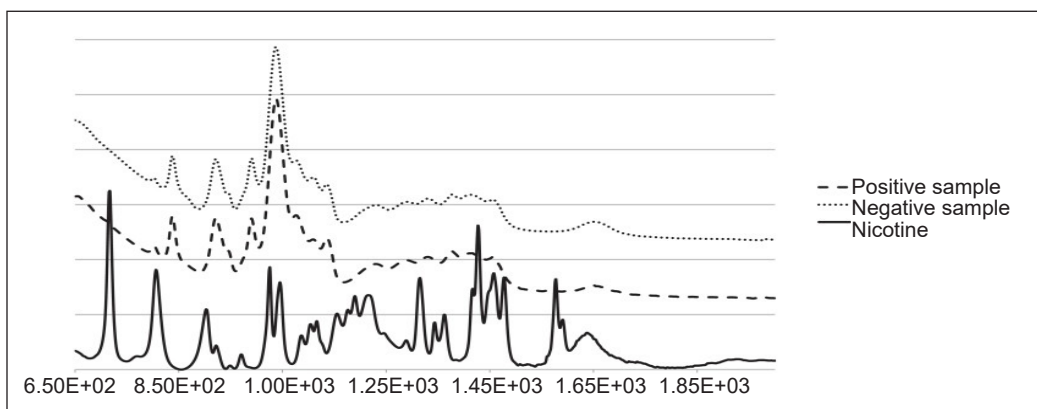
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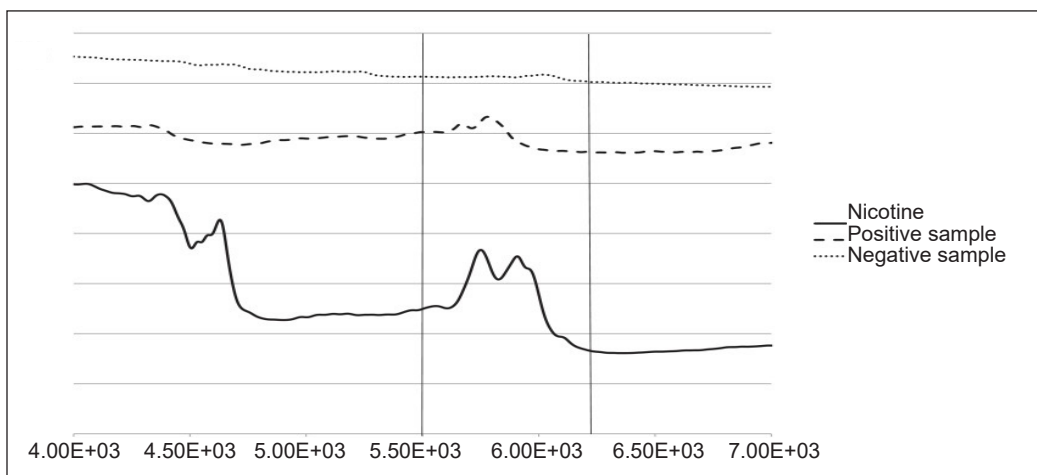
(b)

Figure 5. (a) ATR-IR spectra obtained for nicotine, a positive and a negative sample; and (b) NIR spectra obtained for nicotine, a positive and negative (Deconinck et al., 2016).

peaks below the spectral region of 1000 cm^{-1}. However, many strong nicotine signals were observed within the 2000-650 cm^{-1} spectral region. With the use of NIR, only limited peaks of nicotine were observed.

In addition to e-liquids, a study was conducted on a small-scale sample of the aerosol phase of e-liquid using the FTIR method, which successfully provided an emission profile of volatile organic compounds (VOCs). However, this method is unable to detect nicotine as it only detects smaller molecules such as CO_2, CO, methane, ethane, ethylene, methanol, ethanol, and formaldehyde emitted from the e-cigarette device analyzed with FTIR (Ooi et al., 2019). Traditionally, cigarette smoke has been studied using a high-resolution spectrometer to detect stretching frequencies of a variety of gaseous components, including hydrocarbons, nitrogen, and carbon oxides (Bacsik et al., 2007).

Raman Spectroscopy and Surface-Enhanced Raman Spectroscopy (SERS). The Raman spectroscopy method can also be used for the identification of nicotine. This method requires little to no sample preparation for analysis and is known for its non-invasive approach (Poulsen et al., 2022). As depicted in Figure 6, the Raman spectrum of nicotine polacrilex resin (NPR) from the gum ingredients displays unique nicotine-specific peaks at 1033 and 1052 cm^{-1} (Poulsen et al., 2022).

Apart from the traditional Raman spectroscopy method, the modern method of Surface-Enhanced Raman Spectroscopy (SERS) is also used for the identification of nicotine along with other related compounds. Similarly, two main peaks of nicotine in an aqueous solution can be distinctly observed at 1032 and 1052 cm^{-1}, as shown in Figure 7 (Mamián-López & Poppi, 2013). Anabasine and cotinine also have the same spectral features. The overlapping peaks between the same functional groups are expected to hinder the identification of nicotine in the presence of anabasine and cotinine.
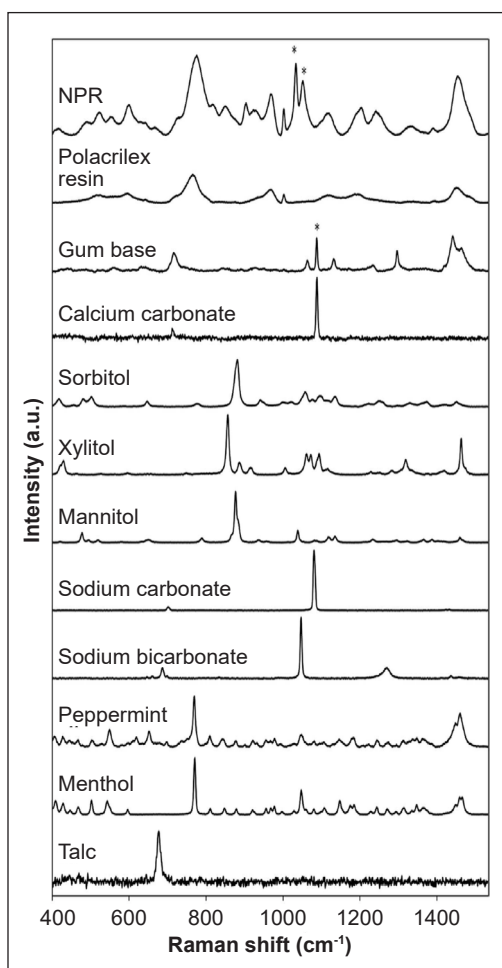

Figure 6. Raman spectra of the individual gum ingredients (Poulsen et al., 2022)
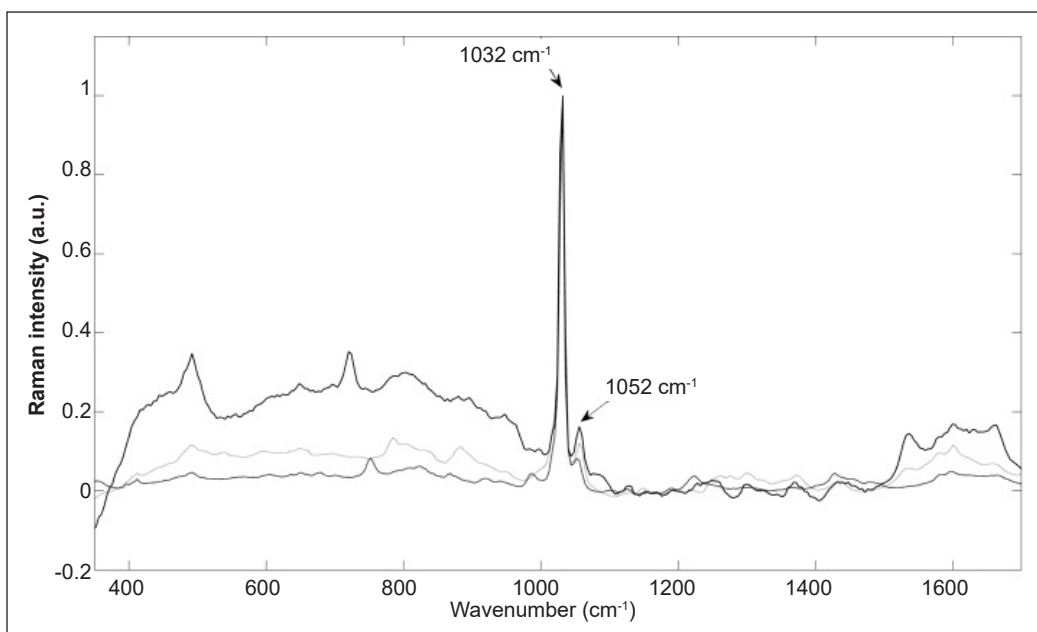
Figure 7. SERS spectra (normalized) of nicotine (solid line), anabasine (dotted line) and cotinine (dashed line) in aqueous solution (Mamián-López & Poppi, 2013)

CONCLUSION

In recent years, analytical methods used in analyzing e-liquids can be categorized into chromatographic and spectroscopic methods, commonly used in this field of study. Among chromatographic methods, the GC-MS technique is the standard method for analyzing volatile compounds in e-liquid samples, including PG, VG, and nicotine. Additionally, HPLC is a well-known technique for identifying and quantifying all soluble compounds, including PG, VG, and nicotine, in a short total analysis time. Several spectroscopic methodologies, such as NMR, FTIR, and Raman analysis, are also available for identification and quantification. However, based on the studied articles, chromatographic methods are the primary option for analyzing nicotine in all e-liquid samples. Limited studies have applied the ATR-FTIR method for identification and quantification, especially in e-liquids found in e-cigarettes. This method has lower analytical performance compared to chromatography methods in detecting nicotine. The modernization of spectrometer design will likely involve the development of new complex statistical models.

ACKNOWLEDGEMENT

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