USE OF A COMPOSITION CONTAINING 1,3-PROPANEDIOL AS E-LIQUID

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ABSTRACT

A composition containing 1,3-propanediol for use as electronic cigarette liquid. A liquid composition for an electronic cigarette, including 1,3-propanediol, as well as at least one compound selected from nicotine, a nicotine substitute, and an aroma, and an electronic cigarette containing this composition.
USE OF A COMPOSITION CONTAINING 1,3-PROPANEDIOL AS E-LIQUID

TECHNICAL FIELD

[0001] The present invention relates to the use of a composition containing 1,3-propanediol as electronic cigarette liquid. It also relates to a liquid composition for an electronic cigarette including 1,3-propanediol as well as nicotine and/or at least one aroma, and to an electronic cigarette containing this composition.

BACKGROUND OF THE INVENTION

[0002] The electronic cigarette market is currently expanding greatly, because it allows the consumer to preserve the ritual associated with the use of the cigarette without suffering the detrimental effects of the harmful substances that it contains.

[0003] The electronic cigarette or e-cigarette works with electricity without combustion. It produces a mist of fine particles, commonly referred to as vapor or artificial smoke, which visually resembles the smoke produced by the combustion of tobacco. This vapor can be flavored (tobacco, mint, fruit, chocolate aroma, etc.) and it may or may not contain nicotine. In correctly manufactured and used e-cigarettes, the aerosol contains, according to available data, many fewer substances that are detrimental to health than the smoke of tobacco; in particular it does not contain solid particles, tar, other carcinogenic substances, or carbon monoxide (CO).

[0004] The e-cigarette comprises three main parts contained in a plastic or metal casing:

[0005] a battery,
[0006] a cartridge or reservoir containing a liquid referred to as “e-liquid,” and
[0007] an atomizer.

[0008] The battery most frequently constitutes the greater part of the e-cigarette in disposable products. In reusable cigarettes, the batteries are “low voltage” (accumulators), rechargeable by USB cable or by a charger. In reusable e-cigarettes, the tube which houses the battery is screwed onto the cartridge containing the liquid. In some models, an indicator light—usually a red or blue diode—is placed at the other end of the tube of the battery.

[0009] The storage device for e-liquid can be in the form of a cartridge (generally made of silicone, PMMA or stainless steel) or of a reservoir (in particular made of PMMA/polyethylene, borosilicate glass or stainless steel), optionally completed by a device for uptake of the liquid by capillarity (in particular, made of silicone, glass fiber, ceramic metal fabric, nylon threads or borosilicate fibers) in contact with the vaporization system. The atomizer makes it possible to convert the e-liquid into a mist that simulates smoke. It consists of a metal coil or mesh which forms a heating resistor. It is more and more often integrated in the rechargeable cartridge. A microvalve sensitive to the low pressure caused by inhalation or a manually triggered contactor ensures the supply of power by the battery to the atomizer. The e-cigarette can be for single use or reusable.

[0010] The e-liquids used are composed mainly of the following constituents:

[0011] synthetic propylene glycol (approximately 65%)
[0012] glycerol (approximately 25%)
[0013] water (5 to 10%)
[0014] aromas and dyes (2 to 5%)

[0015] nicotine (0 to 20 mg/mL).

[0016] Some e-liquids can also contain ethanol in a significant amount (>1%).

[0017] Some products may be free of synthetic propylene glycol. In this case, the objective is to be able to claim products of exclusively plant origin. However, this objective is achieved at the expense of the longevity of the heating resistors which very rapidly become fouled. In addition, the quality of the smoke emitted is far from being appropriate in terms of vapor density, and the organoleptic properties of the liquids are greatly modified, because the release of the aromas is less immediate in the absence of propylene glycol. Moreover, the exclusive use of glycerol requires loading the product with water in order to decrease the viscosity of the e-liquid and thus facilitate the filling of the e-cigarette. But again, the impact of a high water content radically modifies the quality of the vapor released and leads to excessive corrosion of the materials as well as to rapid and excessive consumption of the e-liquid (faster vaporization). Finally, another problem connected with the exclusive use of glycerol lies in the fact that this compound is clearly less vaporizable than propylene glycol, so that its vaporization requires a clearly higher heating temperature which can result in its degradation and the formation of undesirable byproducts such as acrolein.

[0018] Consequently, the use of synthetic propylene glycol in a larger quantity than the glycerol is usually preferable, which does not allow the manufacturers to claim a natural origin for their products. In addition, propylene glycol is obtained by a process which is among the most energy-consuming methods of petrochemistry and consequently has a large environmental footprint (Eissen & al., Angew. Chem. Int. Ed. 2002, 41, 414-436), which is reflected in a high energy consumption and a high production of volatile organic compounds (VOCs) and waste materials. Moreover, synthetic propylene glycol is obtained from propylene oxide by a continuous hydration method, according to the following diagram:

\[ \text{H}_2\text{C} = \text{CH}_2 + \text{H}_2\text{O} \rightarrow \text{HOCH}_2\text{CH}_2\text{OH} + \text{polyglycols} \]

[0019] The production of propylene glycol is accompanied by the formation of secondary products (di-, tri- and tetrapropylene glycols) and unconverted propylene oxide ( Petrochemical Processes: Major Oxygenated, Chlorinated and Nitrated Derivatives—Alain Chauvel, Gilles Lefebvre—Editions TECHNIP—p26), as illustrated below:

\[ \text{H}_2\text{C} = \text{CH}_2 + \text{H}_2\text{O} \rightarrow \text{HOCH}_2\text{CH}_2\text{OH} + \text{polyglycols} \]
Consequently, after purification, the minor and recurrent organic impurities of propylene glycol are di- and tripropylene glycol, as well as propylene oxide whose residual content according to the producers is on the order of 5 to 10 ppm (Propylene Glycol—CIR Expert Panel, June 28-29 2010—Draft Report). Now, propylene oxide is classified by the North-American and European environmental agencies as a carcinogenic and mutagenic compound in animals and as a probable carcinogen in humans. Consequently, it is important to strongly limit exposure to this compound. Thus, the Expert Report and Opinion on e-Cigarettes published by the Office Francais de Prevention du Tabagisme (OFT) [French Office of Prevention of Tobacco Smoking] in May 2013 insists on the need to guarantee absence of carcinogen contaminants in the e-liquids. Consequently, it is important to prevent the presence of a toxic compound such as propylene oxide and to a lesser extent the presence of organic impurities, such as di- and tripropylene glycols, belonging to the family of glycol ethers, strongly disparaged from the toxicological standpoint, which alter the quality of the e-liquids.

A solution to the above-mentioned problems was proposed in the application WO 2013/088230. It consists of replacing synthetic propylene glycol with propylene glycol of plant origin, obtained by catalytic hydrogenation of sorbitol, which itself originates from corn. The propylene glycol is associated with glycerol of plant origin, with nicotine which can be extracted from tobacco leaves, and possibly with aromas of natural origin, resulting in an e-liquid that is entirely of plant origin.

Even if this solution does indeed overcome the drawbacks associated with the use of synthetic propylene glycol, it has now been shown that the vapor density and the aromatic power produced by these e-liquids of plant origin could be improved by replacing propylene glycol with 1,3-propanediol (PDO) and that this effect was particularly pronounced in the absence of glycerol or in an e-liquid composition with low glycerol content. By making it possible to dispense with glycerol, the use of PDO contributes moreover to protecting the heating device of the electronic cigarettes by eliminating the phenomenon of rapid fouling observed in the presence of glycerol. Another advantage connected with the absence of glycerol is that the vapor produced is free of toxic and carcinogenic impurities originating from thermal decomposition of glycerol.

In addition, it was observed that PDO made it possible to obtain nicotine-free e-liquids that recreate the throat hit which is typically felt by the user of a conventional cigarette when the nicotine flows into the mouth. To date, this effect which is greatly sought after by the users of e-liquids has been obtained only by adding several drops of a product based on propylene glycol, glycerol and aromas (E-Liquide Flash® from FLAVOUR ART®) to the e-liquid. However, said product has all the above-mentioned disadvantages connected with the use of propylene glycol and of glycerol.

Today, PDO of plant origin is produced on the industrial level by fermenting glucose. It is currently used as an intermediate in the synthesis of resins, as solvent, moisturizer, preservative in the food, cosmetic, pharmaceutical industries and in body hygiene products, and as component of hydraulic fluids, antifreeze products, brake fluids, coolants, as component of cleaning liquids, of detergents, cosolvent of paints and solvent in the industry of printing inks. Thus, to the knowledge of the Applicant, PDO has never been described as a constituent of e-liquids.

**SUMMARY OF THE INVENTION**

The present invention thus relates to the use of a composition containing 1,3-propanediol and at least one additive selected from the group consisting of glycerol, nicotine, a nicotine substitute and an aroma, as an electronic cigarette liquid.

It also relates to a liquid composition for an electronic cigarette including 1,3-propanediol as well as at least one compound selected from nicotine, a nicotine substitute and an aroma.

Further relates to an electronic cigarette containing this composition.

It also relates to a use of 1,3-propanediol in an electronic cigarette liquid which may or may not contain nicotine, in order to improve the throat hit felt by a user of said liquid and/or the ease of inhaling the vapor produced by said liquid and to a use of 1,3-propanediol in an electronic cigarette liquid containing nicotine, in order to improve the bioavailability of the nicotine.

It moreover relates to a use of 1,3-propanediol, optionally in the presence of glycerol, in an electronic cigarette liquid in order to reinforce the aromatic power and to a use of 1,3-propanediol, optionally in the presence of glycerol, in an electronic cigarette liquid in order to limit or eliminate the formation of coproducts of thermolysis.

Finally, it relates to a use of 1,3-propanediol, optionally in the presence of glycerol, in an electronic cigarette liquid containing nicotine, in order to deliver nicotine in a consistent manner.

**DETAILED DESCRIPTION OF EMBODIMENTS**

In the first application, the term “electronic cigarette” denotes all devices equipped with electrical means that produce vapor and deliver nicotine and/or an aroma. This definition thus encompasses, in particular, personal vaporizers (VP), electronic systems for delivering nicotine (ENDS for “Electronic Nicotine Delivery System,” or ENDD for “Electronic Nicotine Delivery Device”), as well as the elec-
from non-genetically modified plant varieties, such as palm, rapeseed, sunflower seed or copra oil.

[0037] The sorbitol or bio-sourced lactic acid used to produce propylene glycol of plant origin generally originates from sugar-producing or amylaceous plants, such as sugar cane, corn, wheat, potato, sugar beet, rice or sorghum. It is preferable to use sorbitol or lactic acid originating from non-genetically modified plant varieties, such as sugar cane or beet. Even better, the sorbitol or lactic acid is obtained from non-food lignocellulose biomasses such as wood, straw, palm bunches, bagasse, and the cobs of non-genetically modified corn.

[0038] It should be noted that the above-mentioned methods make it possible to obtain not only propylene glycol, but also PDO as co-product, the proportions of which can be adjusted by selecting the reaction conditions appropriately (Nur Dyma bt Saar—Dissertation submitted in partial fulfillment of the requirements for the Bachelor of Engineering (Hons) Chemical Engineering, Universiti Teknologi PETRONAS, May 2013).

[0039] The propylene glycol can represent from 2 to 50% by weight, preferably from 10 to 40% by weight, more preferably from 20 to 30% by weight, with respect to the total weight of the composition.

[0040] It is preferable, according to the invention, that the composition used as e-liquid contains little or no glycerol, that is to say it contains from 0 to 40% by weight of glycerol, preferably from 0 to 20% by weight, for example, from 0 to 5% by weight of glycerol or from 5 to 20% by weight of glycerol. Indeed, it was observed, as indicated above, that the absence of glycerol made it possible to prevent the formation of undesirable byproducts during the heating of the glycerol. It was observed specifically that, at the temperature reached by the resistor of an electronic cigarette, glycerol decomposed into acrolein (Cordoba et al. Proceedings of COBEM 2011-21st Brazilian Congress of Mechanical Engineering, 24-28 Oct. 2011, Natal, R N, Brazil Metzger Brian; Glycerol Combustion—Dissertation of the University of North Carolina, Aug. 1, 2007), a highly toxic compound at very low concentration (Goniewicz et al. Levels of Selected Carcinogens and Toxicants in Vapour from Electronic Cigarettes—TC Online First, published on Mar. 6, 2013 under 10.1136/ tobaccocontrol-2012-050859). Entirely surprisingly, it was also observed that the absence of glycerol made it possible to clearly increase the vapor density and the aromatic power of the electronic cigarette. Advantageously, when present, the glycerol is of plant origin and obtained by the methods described above.

[0041] Except for the above-mentioned constituents, the composition used according to the invention can contain, in addition, at least one compound selected from nicotine, a nicotine substitute (typically a molecule that is not addictive but has a sensory effect similar to that of nicotine), and an aroma.

[0042] The nicotine can be of synthetic or plant origin, and it must preferably meet the purity criteria described in the applicable American Pharmacopeia (USP) and the European Pharmacopoeia (EP). It can also be extracted, in particular, from tobacco leaves or obtained by chemical synthesis. The concentration of nicotine in the composition according to the invention can range from 0 to 50 mg/mL, preferably from 2 to 20 mg/mL.
According to an embodiment, the composition used according to the invention has an aroma content of less than 10% by weight. The aromas can also be aromas of plant or synthetic origin such as those approved in the food and/or pharmaceutical fields, in particular those listed in the EU regulation No. 872/2012 of 1 Oct. 2012 and in the applicable American Pharmacopoeia (USP) and European Pharmacopoeia (EP). The concentration of aromas can range from 0 to 30% by weight, preferably from 1 to 8% by weight, more preferably from 2 to 5% by weight, with respect to the total weight of the composition.

The composition used according to the invention can also include water and/or an alcohol such as ethanol and/or at least one dye. The water and the alcohol can each represent from 0 to 20% by weight, preferably from 1 to 10% by weight, with respect to the total weight of the composition. The dyes can be dyes of plant or synthetic origin, such as those approved in the food and/or pharmaceutical fields and in particular those listed in EU regulation No. 1331/2008 and in the applicable American Pharmacopoeia (USP) and European Pharmacopoeia (EP). The concentration of aromas can range from 0 to 30% by weight, preferably from 1 to 8% by weight, more preferably from 2 to 5% by weight, with respect to the total weight of the composition.

However, it is preferable according to the invention that the composition does not include ethanol and/or does not include water, except for the water optionally contained in the raw materials of which the composition is comprised. Indeed, water can promote the development of pathogenic microorganisms of microbial origin, and its use generally requires the use of preservatives or sterilizing microlift. Moreover, adding water to the e-liquids induces a conversion of the nicotine base into protonated nicotine. Now, it is known to the person skilled in the art that the protonated form of nicotine is clearly less bio-convertible and consequently less addictive than the nicotine base. Thus, 1,3-propanediol makes it possible to formulate highly fluid e-liquids without having to add water purified by reverse osmosis, e-liquids in which the nicotine is present in base form and in its highly bioavailable form, which clearly improves the control of the delivery of the nicotine, particularly during smoking cessation.

Advantageously, the composition according to the invention has a kinematic viscosity at 20°C of less than 200 mPa·s, preferably less than 100 mPa·s, more preferably less than 75 mPa·s, and better yet less than 60 mPa·s, said viscosity being greater than 30 mPa·s, preferably greater than 40 mPa·s, and better than 50 mPa·s.

The invention also relates to an electronic cigarette containing the composition as described above. Said composition is generally arranged in a cartridge firmly connected to a container housing an electrical supply system connected to a device for atomizing the composition.

It also relates to the use of 1,3-propanediol in an electronic cigarette liquid which may or may not contain nicotine, in order to improve the throat hit felt by a user of said liquid and/or the ease of inhaling the vapor produced by said liquid.

It also relates to the use of 1,3-propanediol, optionally in the presence of glycerol, in an electronic cigarette liquid, in order to reinforce the aromatic power.

Furthermore, it relates to the use of 1,3-propanediol, optionally in the presence of glycerol, in an electronic cigarette liquid, in order to limit or eliminate the formation of coproducts of thermolysis.

It also relates to the use of 1,3-propanediol in an electronic cigarette liquid containing nicotine, in order to improve the bioavailability of the nicotine.

Finally, it relates to the use of 1,3-propanediol, optionally in the presence of glycerol, in an electronic cigarette liquid containing nicotine, in order to deliver the nicotine in a consistent manner.

The invention will be understood better in the light of the following examples, which are given purely as illustrations and are not intended to limit the scope of the invention defined by the appended claims.

**EXAMPLES**

**Example 1 (Comparative)**

Preparation and Analysis of a Composition Based on Propylene Glycol of Plant Origin

In a glass mixer provided with a mechanical stirrer, one mixes precisely 10.00 kg of propylene glycol of plant origin (rapeseed) (marketed by the company OiLco under the reference Radino® 4710, USP Pharmacopoeia grade), 1.00 kg of plant glycerol (marketed by the company OiLco under the reference Glycerine 4810, USP and EP Pharmacopoeia grade), 450.0 g of apple fruit aroma (marketed by the company Safisises under the reference PT 128) and 114.50 of plant nicotine (marketed by the company Nicobrand under the reference Nicotine Free Base, Pharmaceutical grade Nicotine ≥99%). The stirring of the mixture (50 rpm) is maintained for 20 minutes. A 500 g sample is collected for analysis.

The mixture is analyzed by gas chromatography coupled to mass spectrometry according to the method described in the publication of Cao et al. (Cao X.L., Corriente J. An isotope dilution headspace method with gas chromatography-mass spectrometry for determination of propylene oxide in food. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2009 Apr.; 26 (4): 482-6.).

At the same time, one proceeds with the analysis in order to determine the content of biologically sourced carbon according to the method ASTM D6866-12.

**Example 2**

Preparation and Analysis of a PDO-Based Composition

The procedure used is identical to that of Example 1, except that the propylene glycol of plant origin is replaced with 1,3-propanediol supplied by the company DuPont & Tate & Lyle L.L.C under the reference Zema® Propanediol.
Results:

[0061] Under the conditions of analysis (sensitivity 0.5 ng/g), no trace of propylene oxide or of di- and tripropylene glycols is detected.

[0062] The content of bio-sourced carbon of the mixture is equal to 99.7%.

Example 3 (Comparative)
Preparation and Analysis of a Composition Based on Synthetic Propylene Glycol

[0063] The procedure used is identical to that of Example 1, except that the propylene glycol of plant origin is replaced with synthetic propylene glycol supplied by the company Dow under the reference Dow® Propylene glycol, USP grade.

Results:

[0064] Under the conditions of analysis (sensitivity 0.5 ng/g), no trace of di- and tripropylene glycols is detected. On the other hand, the content of free propylene oxide is 2.5 mg/kg.

[0065] The content of bio-sourced carbon of the mixture is equal to 9.2%.

[0066] These results show that the synthetic propylene glycol contains undesirable impurities that are not contained in the PDO of plant origin, as illustrated in Example 2.

Example 4
Preparation and Analysis of a Glycerol-Free Composition

[0067] The procedure used is identical to that of Example 1, except that the propylene glycol and the glycerol of plant origin are replaced with PDO of plant origin according to Example 2.

Results:

[0068] Under the conditions of analysis (sensitivity 0.5 ng/g), no trace of propylene oxide or of di- and tripropylene glycols is detected.

[0069] The content of bio-sourced carbon of the mixture is equal to 99.8%.

Example 5
Evaluation of the Efficacy of Various e-Liquids

[0070] The e-liquid compositions prepared in Examples 1 to 4 are evaluated by a trained panel of 10 persons provided with a cigarette of brand Joytech™ and of model eCab™ (December 2013 model). Each reservoir is filled with the same amount of e-liquid (1 mL).

[0071] Under blind conditions, each panelist thus performs a test based on 8 successive drags spaced apart by 20 seconds and each induced by heating for 2 seconds. The evaluation is based on scoring the criteria of vapor density and of aromatic power perceived on a scale from 1 to 10. The switch from one product to another is carried out by each panelist as follows: 5 minutes after the last inhalation, the panelist rinses his mouth with 2 glasses of water of 100 mL each and then drinks 50 mL of water. A rest period of 10 minutes separates the evaluations.

[0072] The averaged results obtained are collected in the following table:

<table>
<thead>
<tr>
<th>Product</th>
<th>Vapor density (score 1 to 10)</th>
<th>Aromatic power (score 1 to 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1</td>
<td>5.8 ± 1.3</td>
<td>5.7 ± 1.5</td>
</tr>
<tr>
<td>Example 2</td>
<td>7.8 ± 1.2</td>
<td>7.9 ± 1.2</td>
</tr>
<tr>
<td>Example 3</td>
<td>5.0 ± 1.4</td>
<td>5.4 ± 1.1</td>
</tr>
<tr>
<td>Example 4</td>
<td>9.0 ± 1.3</td>
<td>8.9 ± 1.2</td>
</tr>
</tbody>
</table>

[0073] It appears clearly that the propylene glycol of plant origin (Example 1) has substantially the same properties as the synthetic propylene glycol (Example 3). On the other hand, PDO (Example 2) has a clearly higher vapor density and aromatic power, which are increased further in the absence of glycerol (Example 4). In comparison to synthetic propylene glycol, it makes it possible moreover to produce e-liquid compositions that have a small environmental footprint and no undesirable impurities such as propylene oxide and its derivatives, including acrolein.

Example 6
Influence of the Nature of the Solvent on the Viscosity and the Nicotine Base Concentration in the e-Liquid Formulations

[0074] In a glass mixer provided with a mechanical stirrer, one mixes precisely 6.00 kg of propylene glycol of plant origin (rapeseed) (marketed by the company Olenon under the reference Radiant® 4710, USP Pharmacopeia grade), 4.00 kg of plant glycerol (marketed by the company Olenon under the reference Glycerine 4810, USP and EP Pharmacopeia grade) and 16.26 g of plant nicotine (marketed by the company Nicobrand under the reference Nicotine Free Base, Pharmaceutical grade Nicotine >99%). The stirring of the mixture (50 rpm) is maintained for 20 minutes. Product A is then obtained. A 200 g sample of A is collected for analysis.

[0075] The same procedure as for product A is used in order to prepare the product B corresponding to a mixture consisting of 5.50 kg of propylene glycol, 4.00 kg of glycerol, 50 g of water purified by reverse osmosis and 162.6 g of nicotine. A 200 g sample of B is collected for analysis.

[0076] The same procedure as for product A is used in order to prepare the product C corresponding to a mixture consisting of 9.837.4 g of 1,3-propanediol supplied by the company DuPont & Tate & Lyle LLC under the reference Zemen® Propanediol and of 162.6 g of plant nicotine (marketed by the company Nicobrand under the reference Nicotine Free Base, Pharmaceutical grade Nicotine >99%). A 200 g sample of C is collected for analysis.

[0077] Finally, product D consists only of 1,3-propanediol supplied by the company DuPont & Tate & Lyle LLC under the reference Zemen® Propanediol.

[0078] Then, the kinematic viscosity of products A, B, C and D is measured.

[0079] In addition, on an Avance Brucker brand apparatus (500 MHz), a proton NMR (Nuclear Magnetic Resonance) spectrum is recorded of products A, B, C, D dissolved beforehand in D₂O (deuterated water). The purpose is to measure the percentage of protonated nicotine in the products. This quantification by proton NMR is carried out on the basis of a calibration curve covering the range of concentration of the protonated nicotine between 5 and 95%.
The results are collected in the following table:

<table>
<thead>
<tr>
<th>Product measurement</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinematic viscosity at 20°C, mPa·s</td>
<td>410.3</td>
<td>53.1</td>
<td>52.3</td>
<td>52.6</td>
</tr>
<tr>
<td>Protonated nicotine concentration, %</td>
<td>34</td>
<td>78</td>
<td>16</td>
<td>—</td>
</tr>
</tbody>
</table>

It is apparent from these tests that product C based on 1,3-propanediol, in which no addition of water purified by reverse osmosis was carried out, has a very advantageous viscosity (<60 mPa·s) reflected in a fluidity that makes it easy to fill an electronic cigarette reservoir.

On the other hand, product A has a very high viscosity, greater than 400 mPa·s). This type of viscous solution cannot be used as e-liquid since it cannot be poured at ambient temperature into the body of the reservoir of an electronic cigarette.

By comparison, due to the presence of water, product B has a fluidity similar to that of products C and D. It corresponds moreover to the solutions currently commercially available on the e-liquid market.

Consequently, it is clear that 1,3-propanediol makes it possible to prepare in a very advantageous manner highly fluid e-liquids without having to add water purified by reverse osmosis, and thus without preservative or without having to use sterilizing microfiltration.

In addition, by allowing the formulation of e-liquids without water, 1,3-propanediol ensures the delivery of the nicotine in the base (unprotonated) form and thus in a highly bioavailable form.

Example 7

Influence of the Nature of the Solvent on the Sensory Properties of the e-Liquid and the Ease of Inhaling the Vapor

The e-liquid compositions B, C and D prepared in Example 6 are evaluated by a trained panel of 40 persons (male sex, age between 25 and 49 years), provided with a cigarette of brand name Joytech™ and of model eCig™ (December 2013 model). Each reservoir is filled with the same amount of e-liquid (1 mL). Under blind conditions, each panelist thus performs a test based on 8 successive drags spaced apart by 20 seconds and each induced by heating for 2 seconds. The switch from one product to another is carried out by each panelist as follows: 5 minutes after the last inhalation, the panelists rinses the mouth with 2 glasses of water of 100 mL each and then drinks 50 mL of water. A rest period of 10 minutes separates the evaluations. The evaluation is based on scoring the following criteria on a scale from 1 to 10:

1) the sensation of the throat hit, that is to say the internal stinging effect on the throat which is conventionally obtained when a smoker takes a drag on a cigarette, which is also perceived when a user of the electronic cigarette inhales a nicotine-rich e-liquid vapor. 2) The ease of inhaling the vapor of the e-liquid.

The averaged results obtained are collected in the following table:

<table>
<thead>
<tr>
<th>Product</th>
<th>Sensation of the throat hit (grade 1 to 10)</th>
<th>Ease of inhaling (grade 1 to 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product B</td>
<td>6.2 ± 1.2</td>
<td>6.9 ± 1.4</td>
</tr>
<tr>
<td>Product C</td>
<td>8.9 ± 0.9</td>
<td>7.9 ± 1.1</td>
</tr>
<tr>
<td>Product D</td>
<td>8.1 ± 1.1</td>
<td>8.1 ± 1.2</td>
</tr>
</tbody>
</table>

It appears clearly that the 1,3-propanediol associated with the nicotine (product C) induces a throat hit that is superior to that of a conventional product consisting of glycerol, propylene glycol, water and nicotine (Product B). Finally, it is of great interest to emphasize that, in the absence of nicotine, 1,3-propanediol alone (product D) induces a significant throat hit that is significantly superior to that of product B.

With regard to the ease of inhaling the vapor induced, e-liquids C and D also are found to be superior to product B.

Example 8

Olfactory and Gustatory Evaluation of the Formulations Based on 1,3-Propanediol with or without Nicotine and Free of Glycerol

A formulation based on nicotine and on 1,3-propanediol containing 15 mg/mL of nicotine is prepared. This formulation as well as a formulation including 1,3-propanediol are subjected under blind conditions to an olfactory evaluation by an expert enologist specializing in the tasting and olfactory characterization of soft drinks and alcoholic beverages. The evaluation includes several different techniques like those used in the context of the evaluations of the major potable alcohols:

Phase 1: Tasting with Nose in a Neutral Tulip Glass

In a first phase, the 2 products were tested in a tulip glass conventionally used for the tasting of cognac. During this evaluation, the notes referred to as first-nose notes and the notes that appear thereafter are recorded for each product. Then, one concludes with an evaluation of the notes present in the empty glass.

Practically speaking, each product is left in the glass. First step: the product is poured into the glass and then smelled. Second step: the glass is covered with a neutral paper and the glass is smelled 12 hours later after having been allowed to rest. Third step: the paper is removed from the glass for two days (this step is carried out when tasting brandies for the purpose of observing the degradations connected with the penetration of air, which generally does lead to degradations).

Phase 2: Tasting with Nose in the Hollow of the Hand

The product to be tested is placed in the hollow of the hand. Before this phase, the hands are rinsed with demineralized water so as not to have any recurrent tastes (odor of the skin, soapy taste associated with a conventional washing or rinsing with tap water with its bleach notes). Then the product is smelled, and in a second step, the product is heated by a massaging action in the hollow of the hand.
Phase 3: Tasting by Nose on the Tip of the Finger and Tasting by Mouth.

A large drop of each product is transferred to the finger and then to the tongue. During this work phase, important nuances from the gustatory standpoint are observed. This crucial step makes it possible to characterize the product correctly.

Phase 4: tasting of the aerosols from the vaporization of the products consumed using an electronic cigarette.

The material used meets the following characteristics:

- BCC clearomizer provided with a 2.2 ohm resistor.
- variable voltage battery set at 3.2 V,
- power delivered 5.7 watt.

Each product is tasted in a new clearomizer. In a first step, the pleasurable notes appear and then the degradation notes. Then, in a second step, the sensations, in particular the gourmet and pleasurable sensations are observed. Finally, the variations during the vaping phase were also observed, in particular in order to measure whether during the different inhalation phases differences appear, in particular with a view to measuring a possible degradation of the products during the heating.

The results are collected in the table below:

<table>
<thead>
<tr>
<th>Product</th>
<th>Tasting by nose</th>
<th>Tasting by mouth</th>
<th>Tasting during vaping</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3 propanediol</td>
<td>Notes of white glue, laden and a creamy aspect tending towards almond paste.</td>
<td>Great softness, no aggressiveness, much roundness.</td>
<td>Dust, brown tobacco, cacao, walnut, cinnamon, hay, caramel. No aggressiveness but the mouth gives one the impression of mold (mushroom), old wood, little persistence, a slight bitterness. As finale, almond and hazelnut notes. No burning at high temperature. The product does not challenge the taste buds. There is no sensation of development of flavors, leaves a point of bitterness as mouth finale after a few minutes. A slightly earthy aspect. First flavor is of smoked fish. A very full-flavored product with dominances of black pepper and presence of mold taste. Gradual modification in the mouth during vaping: the burnt aspect manifests itself increasingly with notes of overheated caramel and carbonic flavors. Much too much bitterness and an overpowering of licorice notes.</td>
</tr>
<tr>
<td>1,3 propanediol + Nicotine (15 mg/mL)</td>
<td>Almond aromas</td>
<td>By mouth, the product is very aggressive. It has pronounced notes of black pepper and a strong nut flavor. Saturation of the flavors. The prickly aspect is too present.</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: these olfactory evaluation tests, performed under blind conditions, bring out the following points:

1. Major differences appear with the same product depending on the tasting mode (by nose, by mouth, or during vaping);
2. While 1,3-propanediol is rather soft and round in the mouth, it rather becomes bitter during vaping.
3. While the addition of nicotine to 1,3-propanediol, at a level of 15 mg/mL, is not detected by nose, the notes delivered in the mouth and during vaping, on the other hand, are completely different from those observed with 1,3-propanediol without nicotine addition.
4. Regardless of the formulation, with or without nicotine addition, the notes detected by nose or mouth do not make it possible to predict the core head notes detected during the vaping of the product.

Example 9

Evaluation of the Thermal Stability of the Formulations Based on 1,3-Propanediol with or without Nicotine, and Free of Glycerol

In the context of these tests, the thermal stability of propylene glycol, of glycerol, of 1,3-propanediol, of nicotine and of their mixture (formulation containing 15 mg/mL of nicotine) was evaluated. The stability of the products and the possible interaction between nicotine and 1,3-propanediol were evaluated by thermogravimetric analysis (TGA) and differential thermal analysis (DTA) on a Q600 TA Instrument apparatus. Thermogravimetric analysis is a thermal analysis method in which the changes of the physical and chemical properties of the materials are measured as a function of the temperature. TGA can yield information on the physical phenomena, such as vaporization or combustion.

Similarly, one can obtain information on chemical phenomena such as dehydration or decomposition. In differential thermal analysis (DTA), the material under study and an inert reference material are exposed to identical thermal cycles. During the analysis, the difference in temperature between the sample and the reference material is recorded. These differences in temperatures monitored versus time relative to the inert reference material provide information on the exothermic or endothermic thermal phenomena undergone by the sample. By integration of the heat flow curve, DTA analysis yields the so-called endothermic enthalpy values when there is energy absorption, or so-called exothermic enthalpy values when energy is released in the form of heat. The endothermic character is connected with a change in the state of the compound (for example, vaporization), while the exothermic character is induced by decomposition reactions or intramolecular and intermolecular chemical reactions.

The thermogravimetric analyzer Q600 from TA INSTRUMENT was used for determining jointly the vaporization temperatures of the products, the enthalpy values and the level of products unvaporized at 350°C. The analysis conditions are the following:

- Test specimen: 50 mg
- Open crucible under air flow: 100 mL/min
- Heating ramp: 10°C/min
- Temperature range: 25 at 350°C. (Temperature conditions representative of normal use and of misuse of an electronic cigarette). Between analyses, the apparatus is cleaned by heating at 600°C. under air flow, in order to eliminate any trace of unvaporized residue deposited on the crucible, the arms of the scale, or the walls of the furnace.
The results obtained are presented in the table below:

<table>
<thead>
<tr>
<th>Product</th>
<th>DTA VapORIZATION TEMPERATURE (°C) (1)</th>
<th>DTA TRANSFORMATION TEMPERATURE (°C) (2)</th>
<th>DTA Residue unvaporized at 250°C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol</td>
<td>260</td>
<td>ND</td>
<td>27.3</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>174</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1,3-propanediol</td>
<td>189</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nicotine</td>
<td>190</td>
<td>ND</td>
<td>1.68</td>
</tr>
<tr>
<td>1,3-propanediol +</td>
<td>202</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nicotine 15 mg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) Endothermic peak
(2) Exothermic peak (reaction and/or decomposition)

Conclusions:

Glycerol vaporizes at 260° C with 27.3% formation of unidentified residues (which may be related to a product of thermal decomposition); propylene glycol vaporizes at a temperature of 170° C without any thermal decomposition; 1,3-propanediol vaporizes at a temperature of 189° C without any thermal decomposition; nicotine vaporizes at a temperature of 190° C, producing a residue after vaporization of 1.08% connected with the presence in the nicotine of an unvaporizable heavy compound; in a mixture, 1,3-propanediol and nicotine vaporize simultaneously at 202° C (1 single vaporization peak observed in DTA) without giving rise to decomposition and/or without reacting with one another.

One observes clearly that the total vaporization temperature of glycerol is very far from that of nicotine. In the same way, the evaporation temperature of propylene glycol is 16° C lower than that of nicotine.

In contrast, the vaporization temperatures of 1,3-propanediol and nicotine considered alone are nearly equivalent. Consequently, a formulation based on 1,3-propanediol and nicotine is perfectly suitable for ensuring a consistent delivery of nicotine in aerosol form in contrast to formulations based on glycerol or propylene glycol or their mixture.

Finally, 1,3-propanediol is a thermally stable solvent of nicotine which vaporizes without interacting with nicotine.

Thus, the thermal stability of 1,3-propanediol as well as the absence of its reaction when heated with nicotine demonstrate its advantage as a formulation base for liquids intended for personal vaporizers.

Example 10 (Comparative)

Evaluation of the Stabilization of Nicotine in Nicotine Base Form by 1H NMR

It is clearly demonstrated in the literature that the most vaporizable form of a nicotine is the nicotine base form, that is to say an unprotonated nicotine. Indeed, nicotine is a molecule that is very sensitive to the acid-base conditions of its environment. Thus, at acidic to neutral pH, it is present in the form of one or more protonated forms that are difficult to vaporize. In contrast, at a basic pH, nicotine is stabilized in the base form, which is easy to vaporize and thus better suited for being administered in aerosol form.
Chemical shifts of the target protons

<table>
<thead>
<tr>
<th>Formulation</th>
<th>H_a</th>
<th>H_b</th>
<th>H_c</th>
<th>H_d</th>
<th>H_e</th>
<th>H_f</th>
<th>H_g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>3.65</td>
<td>3.29</td>
<td>2.66</td>
<td>2.26</td>
<td>8.42</td>
<td>8.39</td>
<td>7.80</td>
</tr>
<tr>
<td>pH 7</td>
<td>3.38</td>
<td>3.14</td>
<td>2.44</td>
<td>2.11</td>
<td>8.37</td>
<td>8.35</td>
<td>7.75</td>
</tr>
<tr>
<td>pH 8</td>
<td>3.17</td>
<td>3.02</td>
<td>2.26</td>
<td>1.99</td>
<td>8.34</td>
<td>8.31</td>
<td>7.72</td>
</tr>
</tbody>
</table>

Conclusions:

It is clearly apparent that nicotine formulated in 1,3-propanediol presents chemical shifts that are nearly identical to those of nicotine at pH 10, that is to say nicotine in unprotonated nicotine base form;

Formulated in propylene glycol and glycerol, nicotine is in an environment whose pH is less than 8, or rather between 7 and 8. Consequently, at this pH, the nicotine base and monoprotonated nicotine forms coexist.

Consequently, nicotine formulated in 1,3-propanediol is essentially present in its most vaporizable form and consequently in the form that is the easiest to be delivered by a personnel vaporizer.

Example 11 (Comparative)

Evaluation of the Aromatic Power and of Throat Hit of Formulations with Aroma and Nicotine Addition that are Based on 1,3-Propanediol or on Propylene Glycol

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Sensation of the throat hit (Grade 1 to 10)</th>
<th>Flavoring power felt (Grade 1 to 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8.8 ± 0.9</td>
<td>9.1 ± 0.8</td>
</tr>
<tr>
<td>B</td>
<td>6.1 ± 1.1</td>
<td>6.5 ± 1.1</td>
</tr>
</tbody>
</table>

Conclusions:

The formulation with added nicotine, which is based on 1,3-propanediol, is shown to be clearly superior in terms of the sensation of throat hit and of aromatic power to a formulation based on propylene glycol;

These results reflect the fact that 1,3-propanediol allows a better delivery of the nicotine and a potentiating effect of the aromas. Thus, 1,3-propanediol, in terms of safety and cost of manufacture, advantageously makes it possible to consider formulations with lighter aroma and nicotine contents.

Example 12 (Comparative)

Evaluation of the Thermal Stability of the Compositions with Added Glycerol, which are Based on 1,3-Propanediol or Propylene Glycol

With a view to evaluating the possible chemical interactions at high temperature between the different constituents of the solvents of the formulations with added nicotine, the thermal stability of different mixtures based on 1,3-propanediol or propylene glycol, with variable glycerol content, was evaluated by DTA-TGA. Thus, these tests were conducted under conditions identical to those of Example 2.

The results obtained are presented below:
Conclusions:

Except for the 20% VG-40% PDO mixture, all the mixtures lead to 2 distinct vaporization peaks corresponding to the evaporation of diol and of the glycerol;

The 20% VG-40% PDO mixture leads to a vaporization of 1,3-propanediol and glycerol, which constitutes an advantage in terms of the homogeneity of the aerosol produced by this mixture;

All the formulations based on propylene glycol lead to the appearance in DTA of exothermic peaks characteristic of intramolecular reactions. Thus, there is a chemical interaction at high temperature (303-304°C) between the constituents of the formulation. These results are similar to the observations made by Jensen et al. (R. Paul Jensen, B. S. Wentai Luo, J. Pankow, R. M. Strongin, D. H. Peyton. Hidden Formaldehyde in E-cigarettes Aerosols. New England Journal of Medicine, 372; 4, pp. 392-393, Jan. 22, 2015) and Bekki et al. (K. Bekki, S. Uchiyama, K. Ohya, Y. Inaba, H. Nakagome, N. Kunugita. Carbonyl Compounds Generated from Electronic Cigarettes. Int. J. Environ. Res. Public Health 2014, 11, 11192-11200) which explain the formation of these byproducts. Indeed, the thermolysis of propylene glycol and glycerol leads to the formation of volatile aldehydes such as formaldehyde, acetaldehyde and acrolein, which react in situ with the glycols present in the e-liquids (propylene glycol and glycerol) in order to form the heavy acetal type compounds;

All the formulations based on propylene glycol lead to the presence of residues that are not vaporizable at 350°C, corresponding to the formation of heavy secondary compounds whose content is between 0.6 and 1.7%);

In contrast, all the formulations based on 1,3-propanediol do not lead to exothermic reactions. The constituents of the formulations are thus stable at high temperature. In contrast to propylene glycol, 1,3-propanediol stabilizes glycerol;

The formulations based on 1,3-propanediol have very low contents of residues that are not vaporizable at 350°C, between 0.01 and 0.3%

In terms of thermal stability, the 1,3-propanediol-glycerol formulations are stable in contrast to the propylene glycol-glycerol formulations which lead to the formation of heavy secondary compounds. It is recalled that the thermal stability of the formulations is an essential prerequisite of formulations intended for personnel vaporizers, with a view to guaranteeing their safety under the conditions of use and misuse of these devices.

Consequently, these results clearly indicate that the formulations based on 1,3-propanediol, which may or may not be combined with glycerol, make it possible to prevent the formation by thermolysis of secondary products such as heavy compounds and volatile toxic aldehydes (acrolein, formaldehyde, acetaldehyde).

1. An electronic cigarette liquid composition containing 1,3-propanediol and at least one additive selected from the group consisting of glycerol, nicotine, a nicotine substitute, and an aroma.

2. The electronic cigarette liquid according to claim 1, characterized in that the composition contains from 0 to 40% by weight, preferably from 0 to 20% by weight, for example, from 0 to 5% by weight or from 5 to 20% by weight, of glycerol.

3. The electronic cigarette liquid according to claim 1, characterized in that the composition has an aroma content less than or equal to 10% by weight.

4. The electronic cigarette liquid according to claim 1, characterized in that the composition contains, in addition, propylene glycol.

5. The electronic cigarette liquid according to claim 4, characterized in that the propylene glycol is obtained from plant raw materials.

6. The electronic cigarette liquid composition according to claim 1, characterized in that the 1,3-propanediol is obtained from plant raw materials.

7. Liquid composition for an electronic cigarette including 1,3-propanediol as well as at least one compound selected from: nicotine, a nicotine substitute, and an aroma.

8. Composition according to claim 7, characterized in that it is free of glycerol.

9. Composition according to claim 7, characterized in that it contains, in addition, propylene glycol, preferably of plant origin.

10. Composition according to claim 7, characterized in that the 1,3-propanediol is obtained from plant raw materials.

11. Composition according to claim 7, characterized in that it contains no water and/or ethanol.

12. Composition according to claim 7, characterized in that it has a kinematic viscosity at 20°C of less than 200 mPa·s, preferably less than 100 mPa·s, more preferably less than 75 mPa·s, and better yet less than 60 mPa·s, said viscosity being greater than 30 mPa·s, preferably greater than 40 mPa·s, and better yet greater than 50 mPa·s.

13. Electronic cigarette containing a composition according to claim 7.

14. A method of improving the throat hit felt by a user of an electronic cigarette liquid and/or the ease of inhaling the vapor produced by an electronic cigarette liquid, comprising adding 1,3-propanediol in an electronic cigarette liquid which may or may not contain nicotine.

15. A method of reinforcing the aromatic power in an electronic cigarette liquid, comprising adding 1,3-propanediol, optionally in the presence of glycerol, to an electronic cigarette liquid.

16. A method of limiting or eliminating the formation of coproducts of thermolysis in an electronic cigarette liquid, comprising adding 1,3-propanediol, optionally in the presence of glycerol, to an electronic cigarette liquid.

17. A method of improving the bioavailability of the nicotine in an electronic cigarette liquid containing nicotine, comprising adding 1,3-propanediol to an electronic cigarette liquid containing nicotine.
18. A method of delivering nicotine in a consistent manner from an electronic cigarette liquid containing nicotine comprising adding 1,3-propanediol to an electronic cigarette liquid containing nicotine.

* * * * *