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(54) **NICOTINE COMPOSITION WITH IMPROVED STABILITY AND TOXICOLOGY**

(57) The present invention relates to a composition comprising a nicotine or nicotine salt liquid formulation in combination with lactic acid for generating an inhalable aerosol in an electronic cigarette, wherein the solvent comprises non-aqueous solvents or solutions with low water content, wherein the water content is less than 5% (w/w). The compositions of the invention are optimized

for improved stability and prolonged shelf life by adjusting protonation state of nicotine and the compositions are further optimized for improved consumers' sensation. The invention further relates to processes of preparing the compositions of the invention as well as methods of administering the compositions.

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Description**FIELD OF THE INVENTION**

5 **[0001]** The present disclosure relates to a liquid composition comprising nicotine and an organic acid wherein the nicotine is presented in protonated form for improved toxicology from decreased degradants, increased stability of nicotine, an extended shelf-life of the composition, and for an optimized user experience.

BACKGROUND

10 **[0002]** Nicotine is a well-known and widely used chemical stimulant which is usually consumed from various tobacco products typically by smoking. The biological effects of nicotine include an increase in heart rate and blood pressure when provided to an individual or animal. Nicotine is also addictive and is reported be associated with satisfying physical and emotional sensations. However, nicotine has not been linked to carcinogenic risk and is used in pharmaceutical nicotine replacement therapy with the aim of smokers quitting cigarettes or switching to a safer consumer product.

15 **[0003]** Chemically nicotine comprises a pyridine and pyrrolidine ring which each contain a nitrogen atom which can be protonated depending on the pH value of the solution. Therefore, nicotine may be present in a solution in different protonation states. The protonation states the free base form of Nicotine (i.e. unprotonated form), a monoprotinated form with a protonation at the N-atom of the pyrrolidine ring and a diprotonated form with an additional protonation at the N-atom of the pyridine ring (see Figure 1). Different levels of protonation of nicotine affect both nicotine stability and user experience during consumption. This is relevant for nicotine replacement therapy (NRT) products which are used to assist patients in transitioning from traditional tobacco products and smoking to address health impairment caused by smoking. For nicotine replacement therapy, different formulations of delivering reduced amounts of nicotine are used to alleviate a subject's withdrawal symptoms and improve the subject's mood. These formulations include gums, patches, lozenges, inhalers, (un)metered dose inhalers (MDI), nasal sprays or electronic cigarettes. The present application refers to nicotine compositions which may be used in electronic devices such as electronic cigarettes, inhalers, nebulizers, soft mist inhalers, and vaporizers to produce an aerosol comprising nicotine.

20 **[0004]** One major challenge of such electronic delivery systems is providing consumers with an acceptable experience, i.e., the vapor of the device has to comply with the consumer's expectations regarding taste and other sensual impressions. The consumer's experience needs to be close to their experience in consumption of traditional tobacco products, as the new pharmaceutical and consumer products are supposed to replace them. Some consumers prefer an aerosol/vapor that resembles the experience of a tobacco product such as a cigarette. Aerosols from e-cigarettes and smoke from tobacco products provide the user with different flavors and the sensations associated with nicotine absorption in the mouth and throat, followed by nicotine absorption in the lungs. These various aspects are described by users in terms of flavor, intensity/quality, impact, irritation/smoothness and nicotine reward. Nicotine contributes to a number of these factors, and is strongly associated with factors such as impact, irritation and smoothness; these are readily perceived by consumers, and electronic delivery devices may offer too much or too little of these parameters for consumers. Different individual preferences also require certain variations of products to accommodate different consumers' expectations.

30 **[0005]** The amount of absorbed nicotine and the absorption speed from the lining of the mouth and lungs affect the experience of the consumer. Nicotine absorption in the mouth is typically obtained from nicotine in the vapor phase. In contrast nicotine absorbed from the lungs is typically obtained from the particulate phase of the aerosol which is inhaled. Each of these factors, and their balance, can strongly contribute to consumer acceptability of an e-cigarette or another inhalation device. Providing means to optimize the overall vaping experience is therefore desirable to e-cigarette manufacturers.

45 **[0006]** A further challenge of providing a nicotine composition is the instability of nicotine and its volatility. Due to the vapor pressure of nicotine in solution as well as degradation of nicotine by e.g. pyrolysis the nicotine content within the nicotine solution gradually declines over time. Instead various nicotine degradation products accumulate in the solution. Hence, manufacturers are interested in nicotine solutions with improved stability and extended shelf life, i.e., nicotine composition which maintain a stable or nearly stable nicotine concentration over an extended period. Furthermore, the accumulation of nicotine degradation products also affects the safety and consumers' experience as well as the potential regulatory approval of these products, as some nicotine degradation products have undesired effects or toxicity.

50 **[0007]** Therefore, the present application presents a solution to the above problems by providing a nicotine composition with improved safety through better toxicity levels measured in harmful and potentially harmful chemicals testing, stability and extended shelf-life, as well as an optimized consumer experience during consumption.

55 **[0008]** Both aspects of the solution can be achieved by optimizing the protonation state of nicotine in the composition of the invention. Patent application CA 2964829 discloses that by protonating at least some of the nicotine present in a solution, the stability of the nicotine solution may be enhanced. By diprotonating at least, a portion of the nicotine, and

specifically at least 5 wt.% of the nicotine present, loss of the nicotine during storage is reduced.

[0009] Protonation of nicotine also strongly affects the consumers' experience. For the nicotine compositions which are used in e-cigarettes or other electrical delivery devices the use of purified, free-base (unprotonated) nicotine is associated with a consumption experience which at least some users consider insufficient and not satisfactory. The experience from using combustion type tobacco products, such as cigarettes is preferred by some tobacco users because they describe a perception of a "throat hit" sensation in their respiratory tract. This "throat hit" experience does not occur when free-base nicotine is provided in the composition. Nicotine in its free-base has high electron density at the N-atoms, this causes a "harsh" sensation, which is off-putting to many users, when introduced to the respiratory tract, or into the oral cavity. Thus, this "harshness" can be mitigated and adjusted to a consumers' experience that allows switching from combustion cigarettes to new safer products by protonation of nicotine by a suitable pH of the composition or by salt formation which binds the nicotine molecules.

BRIEF DESCRIPTION OF THE INVENTION

[0010] In one aspect the present invention relates to a composition comprising a solution of nicotine and lactic acid, wherein the solvent comprises non-aqueous solvents or solutions with low water content, wherein the water content is less than 5% (w/w).

[0011] In another aspect the present invention relates to process for producing the composition of the invention, wherein the process comprises the following steps:

- a. mixing lactic acid and nicotine in a predefined molar ratio,
- b. reaction of the components of the composition to form protonated nicotine.

[0012] In another aspect the invention relates to a method for delivering the composition of the invention to subject, wherein the administration of the composition of the invention involves inhalation of the vaporized composition of the invention.

[0013] In a further aspect the invention relates to a process for improving the user's sensation of a vaporized nicotine solution, the process comprises:

- a. Mixing the composition of the invention comprising nicotine and lactic acid wherein nicotine and lactic acid are present at molar ratio of about 1:2, wherein at least 5% of nicotine is present in a diprotonated form,
- b. Vaporizing the composition,

wherein the improvement of user's sensation is determined according to a VAS questionnaire.

[0014] In a further aspect the invention relates to a composition comprising a solution of nicotine and a weak acid, wherein the solvent comprises non-aqueous solvents or solutions with low water content, wherein the water content is less than 5%w/w, wherein the weak acid is characterized by a pKa-value of less than 4.2.

DEFINITIONS

[0015] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one skilled in the art to which this technology belongs. Although all methods and materials similar or equivalent to those described herein may be used in practice or in testing the present technology, the preferred methods and materials are now described.

[0016] In the description of the methods of the present invention the use of terms for individual steps of the methods such as "first", "second"; "i.", "ii" or "a", "b" etc. does not necessarily imply a required succession of steps. Depending on the method and required time intervals some of these steps may occur simultaneously or in different orders than the listed succession.

[0017] The "bite" or "throat hit" of consumption of the nicotine composition of the invention describes the sensation which is felt by the consumer during consumption of vaporized nicotine compositions. The sensation is dependent on the individual subject and can be recorded using consumer surveys. However, depending on the conditions before and after vaporization in the nicotine composition the sensation can be adjusted, modified, and altered. In particular, the chemistry of the functional groups of nicotine or in nicotine complexes is of relevance for regulating sensation. The consumers' sensation of "bite" or "throat hit" is affected by the protonation state of nicotine. The consumers' sensation may be described as either "harsh" or "smooth".

[0018] The terms "harsh" and "harshness" of the "throat hit" are used synonymously herein and according to the common understanding describe an unpleasant sensory reaction in the respiratory tract of the consumer, including but not limited to burning or itching sensations and/or other unpleasant or painful sensory reactions in the respiratory tract.

Harshness may be quantified, for example, with a visual analogue scale ("VAS"), as well as with other quantification methodologies known in the art such as, for example, where a study participant is asked to rate the level of physical and/or emotional satisfaction he or she felt on a categorical scale, e.g., 0-5, 0-10, strongly like to strongly dislike, etc. The opposite end of the scale of "harshness", i.e., a composition which is not considered to be "harsh" is typically described as "smooth".

[0019] The term "visual analogue scale" ("VAS"), commonly describe a measurement technique that measures a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. Often distinct categorial values are used to describe, sort, and record the characteristic. It is often used in epidemiologic and clinical research to measure the intensity or frequency of various symptoms. For example, the amount of pain that a test subject feels ranges across a continuum from none to an extreme amount of pain. Further, the applied scale for VAS can be a unidimensional measure or alternatively a multidimensional scale. VAS can be presented in a number of ways, including, but not limited to, scales with a middle point, graduations or numbers (numerical rating scales), meter-shaped scales (curvilinear analogue scales), "box-scales" consisting of circles equidistant from each other (one of which the subject has to mark), and scales with descriptive terms at intervals along a line (graphic rating scales or Likert scales). Such "VAS" scales are widely used and commonly accepted in the field and the skilled person is aware of use and design of these scales.

[0020] The terms "deliver", "delivering", "administered" and "administering", are used synonymously herein and refer to providing a quantifiable dose of nicotine in form of an inhalable aerosol. Wherein the aerosol is generated from a liquid nicotine formulation with an electronic cigarette or low temperature vaporizer.

[0021] Administration or exposure to nicotine elicits a well-described "nicotine-related biological effect" which is experienced by the consumer (e.g. subject). The effect includes, but is not limited to, a stimulating effect or a relaxing effect. A stimulating effect may comprise an increased heart rate, an increased blood pressure, or a feeling of satisfaction (e.g., physical satisfaction) of the subject. These nicotine-related biological effects are a key reason keeping smokers addicted to cigarettes, and providing comparable experience from safer nicotine products is imperative in switching smokers to a healthier product.

[0022] "Degree of protonation of nicotine" refers within this application to the relative fractions of nicotine protonation states, i.e., the relative ratios between free-base, monoprotonated and diprotonated nicotine. A low degree of protonation refers to a ratio with predominant free-base nicotine, in contrast a high degree of protonation suggests predominance of diprotonated nicotine.

[0023] The terms "respiratory tract" or "respiratory organs" are used synonymously herein and according to common medical understanding. "Respiratory tract" comprises the "upper respiratory tract" and the "lower respiratory tract" of a subject. The "upper respiratory tract" encompasses the nose, nasal cavities, sinuses, pharynx, and the upper portions of the larynx above the vocal folds (e.g., also known as vocal cords or voice reeds.) The "lower respiratory tract" encompasses the lower portion of the larynx below the vocal folds, trachea, bronchi, bronchioles, and alveoli.

[0024] In the context of this invention "agitate" or "agitation" refer to various mechanical methods of mixing of different substances which may include, but are not limited to, rotating, vibrating, vortexing, swirling, shaking, ultrasonication, stirring, or any movement that causes mixing. Mechanical movements include movements performed by hand or by a rotator.

[0025] The term "organic acid" as used herein, refers to an organic compound with acidic properties (e.g., according to Bronsted-Lowry definition, or Lewis definition). A common class of organic acid is group of carboxylic acids, whose acidity is associated with their carboxyl group, i.e., -COOR. A dicarboxylic acid possesses two carboxylic acid groups. The relative acidity of an organic is measured by its pKa value and one of skill in the art knows how to determine the acidity of an organic acid based on its given pKa value.

[0026] "Nicotine degradation products" herein refer to any and all nicotine degradation products and byproducts which are derived from degradation of nicotine overtime to various possible processes such as, but not limited to, pyrolysis, hydrolysis or similar processes. This includes "minor tobacco alkaloids" as group of compounds which are formed by nicotine degradation. Hence, "nicotine degradation products" does not include other possible impurities from different sources.

[0027] Within this application "shelf life" refers to the storage period under recommended storage conditions (stable cool temperature, low humidity, no exposure to UV-light) during which at least 95% of the original nicotine amount is present in unmodified or undegraded form within the storage container for pharmaceutical applications. Alternatively, "shelf life" refers to the storage period under recommended storage conditions (stable cool temperature, low humidity, no exposure to UV-light) during which at least 80% of the original nicotine amount is present in unmodified or undegraded form within the storage container for consumer applications.

[0028] The terms "electronic cigarette" or "e-cigarette" or "low temperature vaporization device" are used herein, refers to an electronic inhaler that vaporizes a liquid solution into an aerosol mist. These devices are used to simulate and replace the act of tobacco smoking. The liquid solution comprises a formulation comprising nicotine. The design of electronic cigarettes is varied and, in some cases, does not resemble conventional cigarettes. In some cases, the consumer may choose and adjust the administered amount of nicotine. There are generally three essential components of an electronic

cigarette: a cartridge that serves as a mouthpiece and a reservoir for liquid, an "atomizer" that vaporizes the liquid, and a battery. Other embodiment electronic cigarettes include a combined atomizer and reservoir, called a "cartomizer" that may or may not be disposable, a mouthpiece that may be integrated with the cartomizer or not, and a battery.

[0029] The properties of the nicotine composition are relevant for use and administration. This includes "viscosity" of the composition, i.e., the measure of a fluid's resistance to gradual deformation by shear stress or tensile stress.

[0030] "Water activity" is defined herein as the partial vapor pressure of water in a solution divided by the standard state partial vapor pressure of water. The standard state of water is defined as pure water at the same temperature as the solution, i.e., pure distilled water has a water activity of one.

[0031] The liquid composition comprising nicotine which is used for nicotine administration in electronic cigarettes are referred to as "e-liquid" herein.

[0032] The nicotine solution may also comprise flavoring components. In this case the carrier may preferably be propylene glycol. As used herein, the terms "flavor" and "flavorant" refer to compounds and materials which can be used to create a desired taste or aroma in a product for adult consumers. Addition of such compounds may be subject to local regulation and may require regulatory approval. Possible flavorants are selected from the group comprising flavoring ingredients safe for human inhalation, flavor enhancers, bitterness receptor site blockers, sensorial receptor site activators or stimulants, sugars and/or sugar substitutes, and other. They may be synthetic or natural ingredients, or blends thereof.

FIGURE CAPTIONS

[0033]

Figure 1 shows the structure and different possible protonation state of nicotine including the free-base (unprotonated: Nic) form as well as the monoprotionated (Nic⁺) and diprotionated (Nic²⁺) forms of nicotine which are formed depending on the pH value of the composition.

Figure 2 shows basic chemical information for nicotine. Nicotine is a naturally occurring alkaloid with a pyridine and a pyrrolidine group. It has two protonation sites on each nitrogen atom.

Figure 3 shows basic chemical information for lactic acid. Lactic acid has a hydroxyl group adjacent to a carboxylic group, making it an alpha hydroxy acid (AHA). Lactic acid has a known high relative safety of any organic acids based on Permissible Daily Exposure (PDE) data from inhalation studies, and provides a high Safety Factor.

Figure 4 presents a schematical representation of the heating coil. A nichrome coil is wrapped around an organic cotton plant fiber wick in 6 wraps. The heating coil is used for vaporization of the nicotine composition of the invention which is provided within the wick as carrier material. The coil has a resistance of $1.7 \pm 0.1 \Omega$ and a width of 3.5 mm.

DETAILED DESCRIPTION OF THE INVENTION

[0034] The invention of the present application provides an improved composition comprising nicotine for application in electronic cigarettes for both consumer and nicotine replacement therapies. The composition of the invention shows increased stability of nicotine and thus an extended shelf-life of the composition with optimized properties for consumer satisfaction regarding the sensual experience during consumption, i.e., taste and throat hit are optimized for according to consumer expectations.

[0035] In one embodiment the present invention relates to a composition comprising a solution of nicotine (see Figure 2) and lactic acid (see Figure 3), wherein the solvent comprises non-aqueous solvents or solutions with low water content, wherein the water content is at least less than 5% (w/w), preferably less than 4% (w/w), more preferably less than 3% (w/w), more preferably less than 2% (w/w), more preferably less than 1% (w/w), even more preferably less than 0.5% (w/w) and most preferably less than 0.44% (w/w).

[0036] In an alternative embodiment of the composition of the invention the water content is defined according to its water activity. In this embodiment of the invention the water activity is at least below about 0.85, preferably below about 0.5, more preferably below about 0.4 and most preferably below about 0.35.

[0037] Nicotine salts in solution often degrade via pyrolysis and oxidation into pyridine and minor tobacco alkaloids. This makes it difficult to quantify the concentration of nicotine and its minor tobacco alkaloids at a given time in vaporizer e-liquid, making consistent repeatable dosing of nicotine delivery almost impossible under normal use conditions.

[0038] Unwanted nicotine degradation may be addressed by improving device and tank design and minimizing e-liquid exposure to air. Further, appropriate temperature, i.e., cool storage conditions, are also helpful to control and reduce nicotine degradation. Limiting airflow to systems using a blister pack or vacuum packaging may further decrease nicotine

degradation. However, these methods may address only part of the problem of degradation, and none of these methods are currently implementable in a low-waste disposable/recyclable device system.

[0039] Furthermore, small cartridges that minimize the surface area of the solution to interact with air tend to improve nicotine stability, and the larger the cartridge or reservoir, the more interaction and degradation will occur. However, this method of maintaining stable and consistent nicotine delivery is slow, wasteful, cumbersome, and inconvenient, potentially deterring users from switching to vaporizers from more harmful combustibles such as cigarettes.

[0040] Nicotine is prone to oxidation in two locations: the nitrogen-atom within the pyridine ring and the nitrogen-atom within the pyrrolidine ring. The inventors found that nicotine degradation may be reduced by protonation of nicotine due to addition of lactic acid at a 1:2 molar ratio of the nicotine to lactic acid. By adding two protons to the nicotine molecule, oxidation becomes unfavorable, as electrons are tightly bonded to protons donated from lactic acid, which is present in solution as lactate.

[0041] Hence, in the composition of the invention lactic acid is added as a stabilizing agent which is well-known application of lactic acid in drug delivery systems such as metered dose and dry powder inhalers. Lactic acid has both good stability and a favorable toxicity profile, thus it is a well-suited stabilizing agent for administration. Further, lactic acid is a weak acid which can achieve protonation of free-base nicotine (see Figure 1). Preferably, the composition and the pH of the composition are adjusted to achieve protonation of both available protonation sites of the nicotine molecule, i.e., the two N-atoms of both ring structures of nicotine as shown in Figure 1. Lactic acid is added to the composition in sufficient quantity to achieve significant diprotonation of nicotine.

[0042] The improved toxicity through reduced degradants and stability of the composition of the invention is highly relevant for product quality assurance and therefore important for regulatory approval. The degradation of nicotine salts over time can compromise the quality of a vaporizer product or an e-liquid batch. Oxidation can induce, but is not limited to, a color change, viscosity change, foul odor, and inhibit the absorption of nicotine into the bloodstream, potentially deterring users from switching to vaporizers from more harmful combustibles such as conventional cigarettes by creating a less than satisfactory user experience. Moreover, changes in physical and chemical properties of nicotine can cause problems with manufacturing, processing, storing, and using nicotine vaporizers. Further, degradation of nicotine may inhibit the ability for a particular nicotine device to qualify under pharmacopeia standards as a pharmaceutical system.

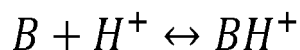
[0043] In one embodiment the composition of the invention comprises protonated nicotine wherein the nicotine is present in the composition in at least 5% diprotonated form as determined by a suitable analytical procedure which is selected from, but not limited to, ¹H NMR spectrometry or calculation based on the pH value of the composition according to Henderson-Hasselbalch equation. Preferably nicotine is present in the composition of the invention in at least 10% diprotonated form, more preferably in at least 15% diprotonated form, more preferably in at least 20% diprotonated form, more preferably in at least 25% diprotonated form, more preferably in at least 30% diprotonated form, more preferably in at least 35% diprotonated form, more preferably in at least 40% diprotonated form, more preferably in at least 45% diprotonated form, more preferably in at least 50% diprotonated form, more preferably in at least 55% diprotonated form, more preferably in at least 60% diprotonated form, more preferably in at least 65% diprotonated form, more preferably in at least 70% diprotonated form, more preferably in at least 75% diprotonated form, more preferably in at least 80% diprotonated form, more preferably in at least 85% diprotonated form, more preferably in at least 90% diprotonated form, even more preferably in at least 95% diprotonated form and most preferably in at least 99% diprotonated form.

[0044] Different analytical procedures are available to determine protonation state of the nicotine within the composition. The skilled person in the field is aware of the available methods and their application. As exemplary methods either ¹H NMR spectrometry or calculation based on the pH value of the composition according to Henderson-Hasselbalch equation may be used.

[0045] ¹H NMR Spectroscopy as based on methodology by Duell et al. may be used to determine nicotine protonation. Briefly, samples of e-liquids are prepared for different test conditions and test compositions at the same nicotine concentrations. The control e-liquid was prepared in propylene glycol : vegetable glycerin (PG : VG, 54 : 46, v/v). Free-base, monoprotated and diprotonated standards are prepared by combining the aliquots of the control sample with suitable base (e.g. t-butylamine : nicotine, 1:1 mol : mol) or with a suitable acid (e.g. acetic acid : nicotine, 5 : 1, mol : mol) to adjust the pH values of the standard samples to achieve the required protonation state.

[0046] NMR spectroscopy is carried out using precision coaxial NMR inserts with experimental parameters as described by Duell et al. Nicotine protonation can be calculated based on difference in chemical shifts between aromatic hydrogens and hydrogens of the methyl (-CH₃) group which connects to protonable nitrogen (N) atoms of the pyrrolidine ring and pyridine ring. NMR will confirm the proportion of the lactic acid that is present in its ionic form.

[0047] Alternatively, the relative fraction of different protonation states of nicotine in solution can be calculated by using the Henderson-Hasselbalch equation based on the pH determination of the composition of the invention. Henderson-Hasselbalch equation is based on the following equilibrium between the protonated and unprotonated states of a general base:



[0048] The above equilibrium is dependent on pH value. Consequently, the fraction of non-protonated nicotine will be predominant at high pH levels whilst a decrease in the pH will see an increase of the fraction of protonated nicotine (mono- and diprotonated nicotine depending on the pH).

[0049] The Henderson-Hasselbalch equation for the above equilibrium is:

$$pH = pKa + \log \frac{[B]}{[BH^+]}$$

[0050] Where [B] is the amount of non-protonated nicotine (i.e. free base), [BH⁺] the amount of protonated nicotine and pKa is the reference pKa value for the pyrrolidine ring nitrogen of nicotine (pKa=8.02). Nicotine is a diprotic base, wherein each of the protonation states: unprotonated, monoprotated and diprotonated have different bioavailability. Hence, an analogous equilibrium and corresponding equation can be noted and calculated for the equilibrium between the mono- and diprotonated forms of nicotine, which describes protonation of pyridine ring nitrogen (pKa=3.12). Based on the above equation the relative fractions of the available nicotine protonation states can be calculated from the pH of the composition. If the relative fraction of protonated nicotine and the total amount of nicotine in the sample are known, the absolute amount of each nicotine protonation state can be calculated.

[0051] In one embodiment of the invention for the composition of the invention to achieve a sufficient degree of protonation the molar mixing ratio between nicotine and lactic acid has to be adjusted. Hence, the composition comprising nicotine according to the invention comprises nicotine in a molar ratio to lactic acid is between about 0.5:2 and about 1.5:2, preferably between about 0.8:2 and about 1.2:2, more preferably between about 0.9:2 and about 1.1:2 and most preferably about 1:2. Accordingly, the higher mixing ration may be needed to achieve near total prevalence of the diprotonated form and even future improved toxicity, stability, and end user acceptance. However, excess lactic acid in the solution that does not bind to the nicotine molecule would be superfluously be present in the composition.

[0052] In one embodiment the composition of the invention may contain different concentrations of nicotine depending on application. The content of nicotine in the composition is between about 1-100 mg/ml, preferably between 10-90 mg/ml, more preferably between 15-90 mg/ml, even more preferably between 30-75 mg/ml, even more preferably between 35-65 mg/ml and most preferably between 40-60 mg/ml. The present nicotine concentration of the composition determines largely the amount of nicotine administered to the subject with each puff of the electronic cigarettes. Thus, the nicotine concentration affects the patient's/end user's experience.

[0053] In one embodiment the nicotine used in the invention may be obtained as an extract from a natural tobacco product.

[0054] In a preferred embodiment of the invention the nicotine used in the invention is synthetic S-nicotine which is obtained from artificial synthesis. Using synthetic S-nicotine provides the advantage of higher purity of nicotine than can be obtained from natural sources. Specifically, this reduces the initial amount of impurities in form of the presence of minor tobacco alkaloids. Hence, using synthetic S-nicotine the nicotine solution of the invention has an improved toxicology profile. Any minor tobacco alkaloids present in the solution of the invention are the direct result of nicotine degradation over time. Starting from a reduced initial amount of minor tobacco alkaloids improves the shelf life of the solution of the invention. The purity of the nicotine used in the composition can be determined by HPLC analysis. Typically, HPLC analysis on anhydrous basis achieves between 99.0 % and 101.0 % of the nominal nicotine amount. Analysis of impurities show a total amount of less than 1.0 %. The composition of the invention comprises initial amounts of minor tobacco alkaloids impurities of less than 0.1% (w/w), preferably less than 0.05% (w/w), more preferably less than 0.01% (w/w), more preferably less than 0.005% (w/w), more preferably less than 0.001% (w/w), even more preferably less than 0.0005% (w/w) and most preferably less than 0.0001% (w/w). Further, an absence of minor tobacco alkaloids will inevitably improve in vitro mutagenicity, cytotoxicity and genotoxicity testing results.

[0055] In one embodiment of the composition the carrier of the nicotine solution may be any suitable solvent such that the nicotine solution can be aerosolized for use. In one aspect the solvent is selected from glycerol, propylene glycol and mixtures thereof. In one aspect the solvent is at least glycerol. In one aspect the solvent consists essentially of glycerol. In one aspect the solvent consists of glycerol. In one aspect the solvent is at least propylene glycol. In one aspect the solvent consists essentially of propylene glycol. In one aspect the solvent consists of propylene glycol. In one aspect the solvent is at least a mixture of propylene glycol and glycerol. In one aspect the solvent consists essentially of a mixture of propylene glycol and glycerol. In one aspect the solvent consists of a mixture of propylene glycol and glycerol.

[0056] In a preferred embodiment the composition of the invention comprising nicotine and lactic acid or other organic acid uses organic solvents with suitable volatility as commonly used for e-liquids. The solvents of the invention are selected

from the group comprising glycerol and propylene glycol. The skilled person in the field is aware of different available solvents which may be used to substitute the above solvents.

[0057] In one embodiment the mixing ratio of the solvents of the composition of the invention can be varied and adjusted depending on application. The ratio of glycerol to propylene glycol in the composition of the invention is between about 80:20% (v/v) and about 20:80% (v/v).

[0058] In an alternative embodiment of the invention the composition of the invention may not contain any solvents. The composition of the invention may comprise nicotine and lactic in solid form as powders for extended storage and subsequent dissolution by the consumer or patient at a later time.

[0059] As stated above the composition of the invention comprises at least 5% (w/w) of diprotonated nicotine. This increases stability of nicotine and extends the storage time of the composition, i.e., the composition the invention achieves an extended shelf life. In one embodiment the shelf life of the composition of the invention is extended to at least 1 month, at least 1.5 months, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 1 year, at least 1.5 years, at least 2 years, at least 2.5 years, or at least 3 years.

[0060] Half-life time of nicotine in the composition of the invention or shelf life of the composition of the invention may be determined by measuring the detectable nicotine concentration after predefined time intervals and thus determine the intermediate loss of nicotine due to degradation. Alternatively, the accumulation of nicotine degradation products may be determined. Accumulation of nicotine degradation products can be measured by determining the amount of minor tobacco alkaloids. It is important to note that if the nicotine used for the formulation is laboratory made S-nicotine, no minor tobacco alkaloids are present at the starting point as very high purity can be achieved for synthetic S-nicotine without natural impurities or degradation products which are derived from nicotine extraction from natural sources. Determination of accumulation minor tobacco alkaloids is in particular relevant to establish best before use dates and for regulatory approval as these degradation products may cause harm to the patient or consumer if present in concentrations exceeding the relevant acceptable thresholds. The concentration of nicotine and minor tobacco alkaloids and other nicotine degradation products can be determined using HPLC, gas chromatography, mass spectroscopy, spectroscopy methods using fluorescence or absorption properties of nicotine and its degradation product and any other suitable approach as known to the skilled person in the field.

[0061] In one embodiment of the composition of the invention the content of minor tobacco alkaloids present is less than 0.01% (w/w) as determined by HPLC, mass spectroscopy or other suitable detection method.

[0062] In one embodiment of the invention the increased stability of the composition of the invention leads to a reduced loss over time of nicotine during storage of the composition of the invention. Loss of nicotine over time is at least less than 8%/month, preferably less than 6%/month, more preferably less than 4%/month, more preferably less than 3%/month, more preferably less than 2%/month, more preferably less than 1.5%/month, more preferably less than 1.0%/month and most preferably less than 0.5%/month.

[0063] In one embodiment the composition of the invention is for use in nicotine replacement therapy (NRT) wherein the composition is administered by inhalation. The composition of the invention is administered using an electronic delivery system as such as an electronic cigarette, a MDI or vaporizer. Wherein administration of the composition involves vaporization by suitable method as known to the skilled person in the field. Typically, vaporization is achieved by applying an electrical current to a wire within a vaporizable solution. The resulting heat of the wire leads subsequently to vaporization of the nicotine composition.

[0064] In one embodiment the composition of the invention achieves a sensorial experience comprising an improved "bite" or throat hit when inhaled as determined according to a VAS survey. As NRTs often lack this key behavioral aspect, and NRTs with this improved experience will increase the quit rate thus making it a more efficacious quit-smoking device.

[0065] A visual analog scale (VAS) assessment is commonly and widely used to record and report a subject's sensations and provide a quantification for individual experience. For instance, it is possible to record the sensation of smoothness/harshness of the "bite" when administering the composition of the invention. In this case "very harsh" and "very smooth" sensation could be defined as the extreme endpoints of a spectrum of possible sensations. Between the defined endpoints the subjects can quantify their sensation on a scale (e.g., 0-100 mm). In this instance higher scores, e.g., indicate a harsher sensation associated with throat hit. Thus, an E-Cigarette Evaluation Questionnaire (CEQ) is used for determining consumers' assessments of the composition of the invention. The composition of the invention is optimized in accordance with the recorded consumers' feedback for improved consumers' satisfaction. A VAS E-Cigarette Evaluation Questionnaire may comprise the following domains: smoking satisfaction, psychological rewards, aversion, enjoyment of respiratory tract sensations, and craving reduction among other domains if required.

[0066] In one embodiment the composition of the invention when used in NRT administers an amount of nicotine between about 0.00325 mg and about 0.325 mg, preferably between about 0.05 mg and about 0.3 mg, more preferably between about 0.1 mg and about 0.2 mg, most preferably between about 0.13 and about 0.14mg per inhalation. The amount of nicotine per inhalation is determined according to Coresta Recommended Method No 81 and ISO 20769:2018. Briefly the conditions of the method are set as follows: 3 second (+/- 0.1 s) duration, 55mL volume (+/- 0.6 mL), and at an

interval of 30 seconds (+/- 0.5 s), repeated 20 times. Further, cigarettes have about 1-2 mg of nicotine that is actively absorbed by the user, and average inhalations have been reported to be between 8-12. If assuming the same user behavior, the inhalation of the NRT to have 0.13/0.14mg per 3 second inhalation equals 1.04/1.12mg (8 inhalations) to 1.56/1.68 mg (12 inhalations), roughly at parity with a cigarette and a likely effective substitute tool for smokers.

[0067] In another aspect of the invention, it relates to a process for producing the composition according to invention. The process of preparing the composition of the invention involves firstly mixing lactic acid and nicotine in a predefined molar ratio according to the above defined ranges (e.g. 2:1) in a dedicated vessel. No additional application of heat or pressure is required for the desired reaction of combining the components and protonation of nicotine to take place. Agitation/Mixing may be required to achieve homogenous mixing and the desired protonation state. Different devices for mixing may be used as required, e.g., contrarotating mixers. Nicotine and lactic acid may be mixed as solid in powder form or as liquids in solution. The result after dissolution of the mixture is a nicotine lactate solution, which is formed via protonation of the nicotine molecule at two sites, the nitrogen molecule of the Pyrroline group and the nitrogen molecule of the Pyrrolidine group.

[0068] It is understood that the primary characteristic that would yield an e-liquid which is incompatible with an ENDS (device) is the viscosity of the e-liquid. Propylene glycol and glycerol are the primary compounds responsible for product viscosity; however, an increased water or ethanol content may significantly decrease product viscosity. E-liquids that are highly viscous may fail to wick to the heating coil at an appropriate rate and, without safety protection in the device, may result in the formation of carbonyls or other thermal degradants of the e-liquid.

[0069] Secondary to viscosity, the solvent properties of the e-liquid for both the device and the primary packaging may result in leachables in the e-liquid. The risk of leachables in e-liquid is thought to be less of a risk to the consumer unless those leachables become aerosolized during use. Leachables of large molecular mass are less likely to become volatile or carried in the aerosol formed during product use.

[0070] Further, the present invention also related to a composition comprising a solution of nicotine and lactic acid, wherein the composition is obtained by the process described above.

[0071] In a further aspect of the invention, it relates to a method for delivering the composition of the invention to subject, wherein the administration of the composition of the invention involves inhalation of the vaporized composition of the invention. As stated above vaporization is achieved within an electrical device by applying heat to the composition of invention and thus the composition is transformed into vapor.

[0072] In another aspect the invention relates to a process for improving the user's sensation of a vaporized nicotine solution, the processes comprises:

- a. Mixing a composition of the invention comprising nicotine and lactic acid according to claims wherein nicotine and lactic acid are present at molar ratio of about 1:2, wherein at least 5% of nicotine is present in a diprotonated form,
- b. Vaporizing the composition,

wherein the improvement of user's sensation is determined according to a VAS questionnaire.

[0073] In another embodiment of the invention instead of lactic acid a different weak organic acid is used in the composition of the invention to achieve protonation of nicotine. The composition comprises a solution of nicotine and a weak acid, wherein the solvent comprises non-aqueous solvents or solutions with low water content, wherein the water content is less than 5%w/w, preferably less than 4%w/w, more preferably less than 3%w/w, even more preferably less than 2%w/w, even more preferably less than 1%w/w, even more preferably less than 0.5%w/w and most preferably less than 0.44%w/w, wherein the weak acid is characterized by a pKa-value of less than 4.2, preferably less than 4.1, more preferably less than 4.0, even more preferably less than 3.9, even more preferably less than 3.8, even more preferably less than 3.7, even more preferably less than 3.6, even more preferably less than 3.5, even more preferably less than 3.4, even more preferably less than 3.3 and most preferably less than 3.2.

[0074] In an alternative embodiment of the composition of the invention the water content is defined according to its water activity. In this embodiment of the invention the water activity is at least below about 0.85, preferably below about 0.5, more preferably below about 0.4 and most preferably below about 0.35.

[0075] In an embodiment of the invention the weak organic acid is selected from the group comprising 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic acid (L), aspartic acid (L), benzenesulfonic acid, benzoic acid, camphoric acid (+), camphor-10-sulfonic acid (+), capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecyl sulfonic acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid (D), gluconic acid (D), glucuronic acid (D), glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid (DL), lactobionic acid, lauric acid, maleic acid, malic acid (-L), malonic acid, mandelic acid (DL), methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid (-L), salicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid (+ L),

thiocyanic acid, toluenesulfonic acid (p), undecylenic acid or combinations thereof as provided in patent application WO2022/152529.

[0076] The composition of the invention can be achieved with a different selection of various weak organic acids provided the acid may achieve protonation of both protonation sites of nicotine and is provided in the composition in a sufficient molar ratio to ensure protonation of nicotine according to the invention. Different weak organic acids will further affect users' sensation when consuming the composition of the invention. For optimized users' sensation appropriate VAS questionnaires need to be performed to determine users' sensation and to adjust the compositions accordingly.

[0077] The increased degree of protonation of nicotine in the nicotine composition of the invention achieves the improved stability and sensory properties for the consumer as described above. Further, the improved stability as well as the use of synthetic S-nicotine with very high purity improves the toxicology of the product as there are less impurities some of which are toxic. However, toxicology is also affected by the means of aerosolization of the nicotine composition of the invention. The key features relevant to generating an aerosol comes from elements of the reservoir, the heating chamber, and the heating element.

[0078] For the composition of the invention aerosolization was achieved using a Nichrome coil with organic cotton plant fiber wick and a silicone coil holder. The coil has a resistance of $1.7 \pm 0.1 \Omega$. The width of the coil is 3.5 mm and the coil is wound around the wick in 6 wraps. Each wrap of the heating coils are arranged with a distance of 1mm between neighboring wraps. This achieves sufficient distance between each wrap to avoid overheating of the nicotine composition during aerosolization. Overheating of the nicotine composition is an important contributor to the formation of toxic compounds during aerosolization. Hence, the described heating coil also contributes to the reduction of toxic components in the aerosol and the improved toxicological properties of the nicotine composition of the invention. For aerosolization a polymer lithium-ion battery is used with 3.7 V and 350 mAh. Further, a 2 ml PCTG liquid chamber is used.

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[0079]

Belushkin, M. et al. (2018). Role of testing standards in smoke-free product assessments. Regulatory Toxicology and Pharmacology. 98. 10.1016/j.yrtph.2018.06.021.

A.K. Duell, J.F. Pankow and D.H. Peyton: Free-base nicotine determination in electronic cigarette liquids by ¹H NMR spectroscopy. Chem Res. in Tox. (2018), 31(6):431-434

EXAMPLES

Example 1: Formulation of test compositions

[0080] The composition of the invention was tested for two new tobacco products with distinct formulations. The formulations are either RED TOBACCO or SMOOTH TOBACCO, which both have relatively high glycerol content (table 1). Glycerol content is typically referred to as a ratio of propylene glycol to glycerol or VG:PG.

Table 1: The glycerol to propylene glycol solvents ratio of the test compositions

FLAVOR	VG:PG
RED TOBACCO	55:45
SMOOTH TOBACCO	55:45

[0081] The components of the test composition are listed below in tables 2 and 3.

Table 2: Composition of Smooth Tobacco E-liquid

% w/w	CAS	FEMA #	Ingredient	Classification
3.52	54-11-5		Nicotine	Active
3.9093	50-21-5	2611	Lactic Acid	Stabilizer
0.4344	7732-18-5		Water	Excipient
41.4504	57-55-6	2940	1,2-Propylene glycol	Excipient

(continued)

% w/w	CAS	FEMA #	Ingredient	Classification
50.3963	56-81-5	2525	Glycerin	Excipient
0.2896			Flavorants	Flavor

Table 3: Composition of Red Tobacco E-liquid

% w/w	CAS	FEMA #	Ingredient	Classification
3.5200	54-11-5		Nicotine	Active
3.9093	50-21-5	2611	Lactic Acid	Stabilizer
0.4344	7732-18-5		Water	Excipient
39.4235	57-55-6	2940	1,2-Propylene glycol	Excipient
50.7900	56-81-5	2525	Glycerin	Excipient
1.9228			Flavorants	Flavor

[0082] The above listed compositions (table 2 and 3) according to the invention were characterized by their physico-chemical properties and tested for nicotine stability and shelf life as well as for harmful or potentially harmful components according to FDA requirements.

[0083] Samples which are subject to stability testing have been stored in long term storage conditions as detailed within ICH Q1A guidance at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\%$ (relative humidity). For each sample conditions different batches were prepared and all measurements were at least performed in triplicates.

Example 2: Harmful and potentially harmful constituents

[0084] A harmful or potentially harmful constituents (HPHC) analysis was conducted to identify a potential increase in degradants or leachables of the initially prepared composition and after a 3 month storage period to test shelf-life. Analysis was performed on the test solutions after aerosolization. Aerosolization was achieved using a Nichrome coil with organic cotton plant fiber wick and a silicone coil holder. The coil has a resistance of $1.7 \pm 0.1 \Omega$. The width of the coil is 3.5 mm and the coil is wound around the wick in 6 wraps. For aerosolization a polymer lithium-ion battery is used with 3.7 V and 350 mAh. A schematical representation of the heating coil is shown in Fig. 4.

[0085] In accordance with FDAs guidance to industry issued in June 2019 (*Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems*, FDA 2019), the inventors evaluated the new tobacco products for the risk of harmful or potentially harmful constituents. A number of FDA's indicative list of 31 compounds includes a number of compounds which are added as part of the product formulations including; glycerol, menthol, nicotine, propylene glycol and vanillin. Complete testing on all of FDA's list of HPHCs were measured in the aerosol generated using the applicant's device as disclosed in US provisional application US 63/431,735 filed on September 19, 2022, and following the below standard regime. US provisional application US 63/431,735 is hereby included by reference into the present application regarding the technical specifications of the applied device for vaporization.

[0086] The amount of nicotine as well as harmful and potentially harmful constituents per inhalation is determined according to Coresta Recommended Method No 81 and ISO 20769:2018. Briefly the conditions of the method are set as follows: 3 second (± 0.1 s) duration, 55mL volume (± 0.6 mL), and at an interval of 30 seconds (± 0.5 s), repeated 20 times (Puffing regime see table 4).

[0087] As it stands, there are currently no accepted or recognized specifications/standards for intense puffing regimes for ENDS products. The following justification; therefore, draws on previously conducted studies relating to user topography. Belushkin et al., (2018) proposes that this regime is reasonable with regard to the robustness of the product's aerosol emissions.

Table 4: Puffing regimes applied for aerosol sampling

REGIME	VOLUME	DURATION	PERIOD	NUMBER	PROFILE
STANDARD	55mL $\pm 0.6\text{mL}$	3 see ± 0.1 see	30 see ± 0.5 see	20	Square wave

[0088] The standard regime represents an airflow of 1.1 l/min air

Example 3: Shelf-life verification (stability study) for compositions of invention

[0089] The purpose of the stability study is to establish, based on testing a minimum of three (3) batches of the drug product, a shelf-life and label storage instructions applicable to all future batches of the new tobacco product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a production batch will remain within specification throughout its shelf life.

[0090] A 3-month shelf-life study was performed to evaluate the quality of the applicant's products over their intended shelf-life. Samples are to be assessed for; pH, appearance, nicotine assay and nicotine-related substances at predefined intervals through shelf-life. Additionally, water activity, total yeast and mold, total aerobic microbial count and confirmation of absence of a number of microorganisms were performed at the start and end of product shelf-life test periods. Due to the anti-microbial properties of glycerol, propylene glycol and nicotine, and the absence of added water to the formulations of the new tobacco products, it was anticipated that the microbial specification of the product will be met without concern.

Physicochemical Properties of the Samples

[0091] Three attributes were assessed as part of the physical testing of the e-liquids during stability: pH, water activity and appearance. Monitoring changes in pH over time can indicate chemical change in the product as a result of degradation or leachable from the packaging. Appearance was monitored at each timepoint to ensure no visible degradation of the product occurs. Within a 3 month test period no degradation was observed all test samples showed clear liquids which were free from any particles. The color of the liquid was orange for Red Tobacco batches and yellow for Smooth Tobacco batches. Quantified physicochemical information on the average of test batches are provided below in table 5.

Table 5: Physical properties of sample formulations

	Mean Nicotine Amount (mg/g)	Mean pH-value	Mean Water Activity
Red Tobacco	31.81±0.7172	4.14±0.0156	0.32±0.0133
Smooth Tobacco	32.15±0.1205	4.11±0.0464	0.34±0.0097

Chemical Testing

[0092] Two primary chemical tests were conducted as part of the shelf-life study. An assay of nicotine was performed to ensure that the product properties remain within an acceptable tolerance throughout product shelf life. A significant decrease in nicotine assay may indicate an increase in the level of related substances. Related substances will also be monitored throughout product shelf life. Nicotine n oxide, cotinine and myosmine are three nicotine degradants (due to oxidation, biological activity and reaction with water respectively). Nicotine n oxide and cotinine are understood to be the major related substances which are likely to form over the course of the products shelf-life. According to the observed data, the data indicate clearly that there is no concern of safety issues relating to an increase in nicotine related substances. Nicotine impurities were certified as part of quality control and material sourcing/certification. Nicotine complying with compendial specifications is used in the manufacture of the new tobacco products. Additionally, evaluation of N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) levels in the aerosol were performed as part of the stability testing. NNN and NNK are tobacco-specific nitrosamines (TSNAs) classified as carcinogenic chemicals. The aim of the NNN and NNK assessment is to confirm the product safety.

[0093] Below tables 6 and 7 present the obtained stability data for tested nicotine formulations. Nicotine degradants (nicotine n oxide, cotinine and myosmine) and TSNAs (NNN and NNK) could not be detected in the samples. The data clearly indicate that the compositions of the invention are at least stable for 3 months without detrimental loss of nicotine or accumulation of toxic degradation products of nicotine. The presented data indicate stable nicotine within the test samples with only minimal loss of nicotine over the observation period.

Table 6: 3 months stability of Red Tobacco samples (40 mg/ml Nicotine)

	Nicotine (mg/g); t=0	Nicotine (mg/g); t= 3 months	Loss after 3 months	Average loss
Sample 1	33.82	31.11	8.0	5.4%±0.0248
Sample 2	33.47	32.44	3.1	
Sample 3	33.6	31.88	5.1	

Table 7: 3 months stability of Smooth Tobacco samples (40 mg/ml Nicotine)

	Nicotine (mg/g); t=0	Nicotine (mg/g); t= 3 months	Loss after 3 months	Average loss
Sample 1	32.42	32.07	1.1	2.8%±0.0175
Sample 2	33.66	32.12	4.6	
Sample 3	33.14	32.26	2.7	

[0094] Sample compositions were tested for further possible impurities, harmful or potentially harmful constituents. The further tested constituents are listed below in table 8. The constituents as listed in table 8 were either not detected within the sample compositions or detected at below the relevant threshold level. Thus, the tested sample compositions are acceptable according to the toxicology review.

Table 8: List of tested harmful or potentially harmful constituents

Acetaldehyde	Acetyl propionyl	Acrolein	Acrylonitrile	Benzene
Benzaldehyde	Benzyl acetate	Butyraldehyde	Cadmium	Chromium
Cinnamaldehyde	Crotonaldehyde	Diacetyl	Diethylene glycol	Ethyl acetate
Ethyl acetoacetate	Ethyl vanillin	Ethylene glycol	Formaldehyde	Furfural
Glycerol	Glycidol	Isopentyl acetate	Isobutyl acetate	Lead
Menthol	Methyl acetate	N-Butanol	Nickel	Nicotine
4-(methylnitrosamino)1-(3-pyridyl)-1-butanone (NNK)	N-nitrosornicotine (NNN)	Propionic acid	Propylene glycol	Propylene oxide
Toluene	Vanillin			

Microbial testing

[0095] Water activity and evaluation of bioburden and confirmation of the absence of certain microorganisms was performed at the start and end of product shelf-life test periods. Compendial limits for TAMC, TYMC, an absence of *S. Aureus*, *P. Aeruginosa* and bile tolerant gram-negative bacteria have been applied to the new tobacco products specifications. It is understood that formulations comprising propylene glycol, glycerol and nicotine have inherent antimicrobial properties, this may be due to the humectant properties of propylene glycol and glycerol in combination with nicotine's antibacterial properties for gram-negative bacteria. In contrast to other types of tobacco product, products containing tobacco (as opposed to just nicotine) and which have a water activity greater than 0.85 will likely present an increased risk of microbial viability.

Claims

1. A composition comprising a solution of nicotine and lactic acid, wherein the solvent comprises non-aqueous solvents or solutions with low water content, wherein the water content is less than 5% (w/w).
2. The composition of claim 1 wherein the nicotine is present in the composition in at least 5% diprotonated form as determined by a suitable analytical procedure which is selected from ¹H NMR spectrometry and calculation based on the pH value of the composition according to Henderson-Hasselbalch equation.

3. The composition of any one of the preceding claims wherein the composition comprises nicotine in a molar ratio to lactic acid is between about 0.8:2 and about 1.2:2.
4. The composition of any one of the preceding claims wherein the content of nicotine is between about 1-100 mg/ml.
5. The composition of any one of the preceding claims wherein the solvent comprises glycerol or propylene glycol, wherein preferably the glycerol and propylene glycol are present at a ratio of between about 80:20% (v/v) and about 20:80% (v/v)
6. The composition according to claims 1-4 wherein the composition does not comprise a solvent.
7. The composition of any one of the preceding claims wherein the composition comprises synthetic S-nicotine.
8. The composition of any one of the preceding claims wherein the storage half-life time of nicotine is increased to at least 1 month.
9. The composition according to claim 8 wherein the content of minor tobacco alkaloids present is less than 0.1% (w/w) as determined by HPLC, mass spectroscopy or other suitable detection method.
10. The composition according to any one of the preceding claims for use in nicotine replacement therapy (NRT) wherein the composition is administered by inhalation.
11. The composition for use according to claim 10 wherein the sensorial experience comprises an improved "bite" or throat hit when inhaled as determined according to VAS consumer survey.
12. The composition for use according to claims 10 and 11, wherein the administered amount of nicotine is between about 0.00325 mg and about 0.325 mg, where the inhalation is tested according to Coresta Recommended Method No 81 and ISO 20769:2018, wherein the applied conditions are 3 second (+/- 0.1 s) duration, 55mL volume (+/- 0.6 mL), and at an interval of 30 seconds (+/- 0.5 s), repeated 20 times.
13. A process for producing the composition according to any of the claims 1-9 comprising:
 - a. mixing lactic acid and nicotine in a predefined molar ratio,
 - b. reaction of the components of the composition to form protonated nicotine.
14. A method for delivering the composition according to any of the claims 1-9 to subject, wherein the administration of the composition of the invention involves inhalation of the vaporized composition of the invention.
15. A process for improving the user's sensation of a vaporized nicotine solution, the process comprises:
 - a. Mixing the composition according to claims 1-9 comprising nicotine and lactic acid wherein nicotine and lactic acid are present at molar ratio of about 1:2, wherein at least 5% of nicotine is present in a diprotonated form,
 - b. Vaporizing the composition,wherein the improvement of user's sensation is determined according to a VAS questionnaire.

Figure 1

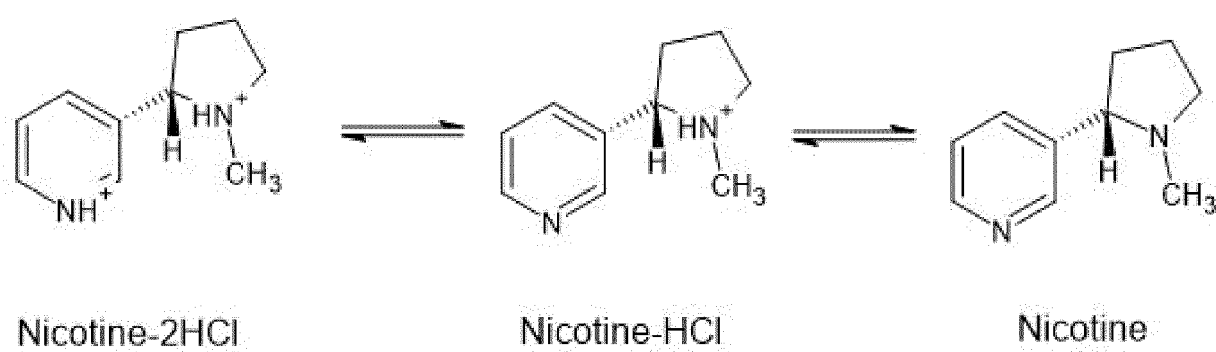


Figure 2

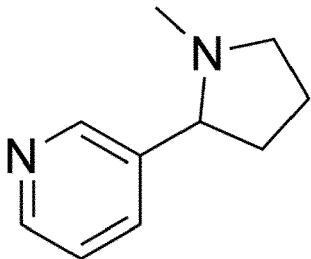
Chemical Name	Nicotine	Structure
IUPAC Name	3-(1-methyl-2-pyrrolidinyl)pyridine	
CAS	54-11-5	
FEMA	-	
Empirical Formula	C ₁₀ H ₁₄ N ₂	
Molecular Mass	162.23 g/mol	

Figure 3

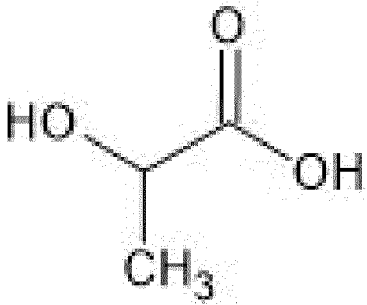
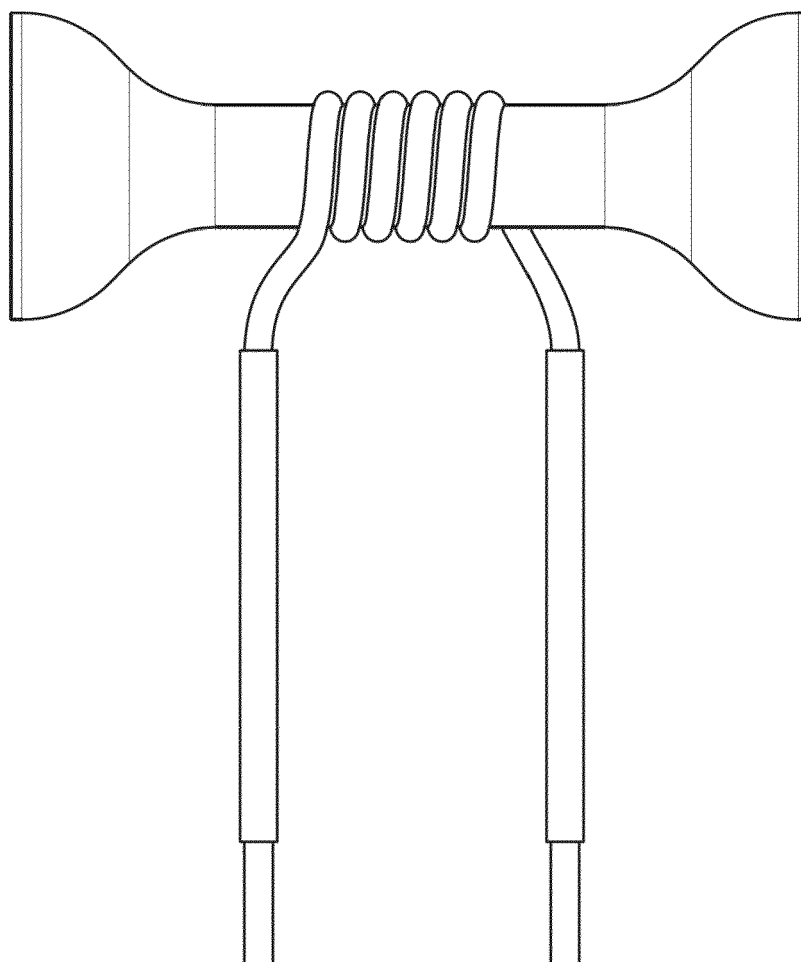
Chemical Name	Lactic Acid	Structure
IUPAC Name	2-hydroxypropanoic acid	
CAS	-	
FEMA	2611	
Empirical Formula	C ₃ H ₆ O ₃	
Molecular Mass	90.08g/mol	

Figure 4





EUROPEAN SEARCH REPORT

Application Number

EP 23 18 6556

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 11 202 470 B2 (NJOY LLC [US]; NJOY INC [US]) 21 December 2021 (2021-12-21) * claims 1,18 *	1-15	INV. A24B15/167
A	US 2006/018840 A1 (LECHUGA-BALLESTEROS DAVID [US] ET AL) 26 January 2006 (2006-01-26) * the whole document *	1-15	
A	US 2022/007715 A1 (BRUTON CONNOR [GB] ET AL) 13 January 2022 (2022-01-13) * the whole document *	1-15	
			TECHNICAL FIELDS SEARCHED (IPC)
			A24B
The present search report has been drawn up for all claims			
Place of search		Date of completion of the search	Examiner
The Hague		22 January 2024	Gzil, Piotr
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
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