

"LIQUID COMPOSITION FOR INHALATION FOR ELECTRONIC CIGARETTES"

DESCRIPTION

Application field of the invention

The present invention relates to a liquid composition for inhalation for electronic cigarettes.

Background art

The use of electronic cigarettes, so-called "vaping", is now a widespread practice all over the world as an at least partial substitute for smoking cigarettes. In fact, it is known that cigarette smoke causes serious damage to health, not so much because of nicotine, which is also a highly toxic substance, but because of the combustion by-products, such as polycyclic aromatic hydrocarbons, tar, and carbon monoxide, often having a marked carcinogenic effect.

There are two types of alternative smoking on the market. A first type consists of systems which include heating tobacco at a controlled temperature (generally not higher than 350°C), so as to avoid the harmful effects of high-temperature combustion. The second type is given by so-called "electronic cigarettes" which vaporize a liquid also comprising, in addition to a base adapted to give a sufficiently dense body to the vapor released, a

controlled amount of nicotine and various types of flavorings.

The first type, with heated tobacco, is more similar to traditional smoking, but despite the lower combustion temperatures some toxic substances contained in the tobacco in addition to nicotine are still released. A typical example is nitrosamines.

Electronic cigarettes are safer since they do not release such toxic or carcinogenic substances, apart from a controlled amount of nicotine, which can be added to the composition in order to give the desired effect of stimulating the nicotinic receptors to the smoker. The possibility of flavoring the composition in various manners is a further attraction.

However, even electronic cigarettes are not without toxicity. In fact, the basic composition mostly consists of a mixture of propylene glycol and glycerol which impart, especially the former, a toxicity on respiratory tract cells.

Therefore, the problem of being able to further lower the toxicity of a composition for inhalation by electronic cigarette so as to make the prolonged consumption thereof much safer is still felt.

The electronic cigarettes currently on the market are born from a Chinese inventor with the aim of providing smokers

with an alternative tool characterized by less toxicity while maintaining a high efficacy in the administration of nicotine. 15 years after its worldwide diffusion, it can be considered that if the first characteristic was largely centered, albeit with the limits set out above, the second was definitely lacking. According to the Public Health of England and the Royal College of Physicians, e-cigarettes on the market are 95% less dangerous than conventional cigarettes. However, if on the one hand there is a growing scientific literature supporting the ability of the electronic cigarette to offer a valid tool in the fight against smoking, currently only a minority of smokers have given up the habit of smoking. This limitation of the effectiveness of the electronic cigarette as a tool for smoking cessation finds several causes, including the incorrect perception of danger in consumers, the sensory experience that is not entirely satisfying and above all the nicotine release profile. The traditional cigarette has an exceptional ability to deliver nicotine to the nicotinic receptors in terms of quantity and speed. On the contrary, the pharmacological devices currently on the market for the controlled release of nicotine have performances that are not comparable to traditional cigarettes. Being able to increase the rate of nicotine release and delivery to the central nervous

system via e-cigarettes can therefore be a considerable tool in helping smokers transition to less harmful products.

Cigarette smoke is a colloidal dispersion composed of solid elements, liquids and airborne gases. A conventional cigarette contains on average 8-10 mg of nicotine and about 10-20% of this is absorbed by the smoker. The high pH of the processed tobacco blends allows to deprotonate a high amount of nicotine, which is released in the form of gas during combustion. The combination of these elements (high concentration, free form, gaseous state) generates a mix of ideal conditions for a rapid and efficient nicotine uptake profile.

The formulations for electronic cigarettes are normally composed of a mixture of propylene glycol, vegetable glycerin and nicotine. Unlike cigarette smoke, the aerosol produced by these electronic devices is characterized by the presence of droplets (drops of liquid). Nicotine is present in the form of free nicotine (free base) or its salt. When present in free form, nicotine tends to exit the droplets, in the form of gas or vapor. This mixture tends to deposit nicotine in airborne form on the oropharyngeal mucous membranes and in the upper airways and the trapped one of the droplets at the alveolar level. The particle size is a decisive element in modulating the

nicotine deposition efficiency as particles that are too large tend to deposit on the mucous membranes of the respiratory tree (decreasing the speed and efficiency of absorption) while too small particles sequester the nicotine present, as they tend to be exhaled with the breath. The particle size distribution depends in turn on a number of aspects including the characteristics of the device and the components of the mixture.

An ideal device will be able to produce an aerosol characterized by particles of the right size and an optimal flow of particles to deposit the right fraction of nicotine at the oropharyngeal and lung level, where the first site is important for correct sensory perception and the second is important for high absorption.

The formulation of the consumable liquid component will have to be optimized to maximize the bioavailability of nicotine. Some of the factors affecting this parameter include the polarity of the particles, the size of the particles, the shape of the nicotine (free or complexed), the excipients and the pH of the solution.

Summary of the invention

The aforesaid technical problem is substantially solved by a composition comprising the technical features set out in one or more of the appended claims, the definitions of which form an integral part of the present description for

the purpose of sufficiency of description.

Therefore, the present invention relates to a composition for inhalation by electronic cigarette comprising the following components:

- | | |
|-------------------------------|-------------------|
| a) water | 25-40% by weight |
| b) 1,3-propanediol | 30-50% by weight |
| c) glycerol | 20-30% by weight |
| d) a preservative | 0.1-5% by weight |
| e) optionally, nicotine | 0.2-6% by weight |
| f) optionally, a flavouring | 0-10% by weight |
| g) optionally, a cyclodextrin | 0.1-5% by weight. |

The invention further relates to a kit comprising one or more doses of the composition of the invention and one or more doses of flavorings.

Further features and advantages of the present invention will become more apparent from the indicative and thus non-limiting description of preferred, but not exclusive embodiments of the invention.

Detailed description of the invention

The present invention relates to a base composition for inhalation by electronic cigarette which does not contain propylene glycol and comprising the following components:

- | | |
|--------------------|------------------|
| a) water | 25-40% by weight |
| b) 1,3-propanediol | 30-50% by weight |
| c) glycerol | 20-30% by weight |

- d) a preservative 0.1-5% by weight
- e) optionally, nicotine 0.2-6% by weight
- f) optionally, a flavouring 0-10% by weight
- g) optionally, at least
a cyclodextrin 0.1-5% by weight.

The water is preferably purified water FU. Its main function is to modulate the polarity of the aerosol particles, break down the toxicity of the mixture and increase the bioavailability of nicotine.

The 1,3-propanediol (component b)) acts as a viscosifying agent, increases the share of deprotonated nicotine by increasing the pH of the solution, bind the water particles by modifying the properties of the mixture both biologically and in the tank, and convey the aromas with high efficiency.

Glycerol (component c)) is preferably vegetable glycerol, whose main function is to modulate the body of the aerosol, defining its hygroscopicity and osmolarity.

The preservative (component d)) is preferably sodium benzoate.

Cyclodextrins (component g)) have the function of enhancing aromas and modulating the perception and bioavailability of nicotine.

The flavorings (component f)) can be of any type normally used for electronic cigarettes, such as fruit, tobacco,

mentholated flavors, or mixtures thereof. The flavorings can be added to a base composition which does not contain them directly by the smoker.

The greater amount of water compared to the compositions for conventional electronic cigarettes allows to decrease the toxicity of the composition.

The substitution of propylene glycol (used in conventional compositions) with 1,3-propanediol also produces a substantial decrease in the toxicity of the composition.

Furthermore, the high amount of water, by modulating the polarity of the aerosol particles, increases the bioavailability of nicotine, making the product extremely effective from the point of view of pharmacokinetics, but in itself an excessive increase in water can lead to malfunctions and losses of liquid from the device. These possible disadvantages are counterbalanced by the presence, in appropriate quantities, of 1,3-propanediol, which by forming hydrogen bonds with water causes a change in the surface tension and a different capillarity behavior.

In preferred embodiments, the basic composition for inhalation via e-cigarette that does not contain propylene glycol comprises:

- | | |
|--------------------|------------------|
| a) water | 29-33% by weight |
| b) 1,3-propanediol | 38-43% by weight |

- c) glycerol 22-28% by weight
- d) a preservative 0.1-5% by weight
- e) optionally, nicotine 0.2-6% by weight
- f) optionally, a flavouring 0-10% by weight
- g) optionally, at least
a cyclodextrin 0.1-5% by weight.

EXPERIMENTAL PART

In order to study the potential skin irritation of the compositions of the invention, a sample of the composition was applied as such to reconstructed human epidermis (RHE), the cell viability of which was then evaluated by MTT test.

The reconstructed human epidermis consists of normal human keratinocytes grown on an inert polycarbonate filter at the air-liquid interface in a chemically well-defined growth medium.

The chemical base of the test is the reduction of MTT, a yellow substance in solution, to form purple formazan crystals. Such a reduction process mainly occurs in the mitochondria and is highly dependent on the activity of the mitochondrial enzyme succinate dehydrogenase. As a result of these metabolic processes, purple formazan crystals appear within some hours, which can be dissolved in isopropanol. The absorbance of the solubilized crystals can be measured at the wavelength 540 nm and is

proportional to the number of living cells in a very wide linear range.

The reduction of the cell viability of the tissues treated with the test sample with respect to the negative control is used to predict the potential for skin irritation.

For this purpose, 3 RHE tissues were treated with the tested product and 3 were treated with 5% sodium dodecyl sulfate (SDS) (positive control). 3 untreated RHE tissues (kept in D-PBS during the incubation period) were used as a negative control. The tested sample is considered irritating to the skin if the cell viability of the tissues upon the treatment is $\leq 50\%$.

The test was performed following the guidelines of UNI EN ISO 10993-10:2013.

Pre-incubation

The RHE tissues were left in growth medium for at least 2 hours (37°C, 5% CO₂) before treatment.

Treatment

The RHE tissues were treated for 15 minutes with 30 µl of substance according to the following pattern:

- Negative control DPBS
- Positive control 5% SDS
- Tested sample.

Each experiment was conducted in triplicate.

Washes

The RHE tissues were repeatedly washed with DPBS, in order to eliminate all traces of the substances used for the treatments.

Post-incubation

The RHE tissues were transferred to the growth medium for 42 ± 2 hours (37°C , 5% CO_2).

MTT Test

The RHE tissues were treated with MTT (1 mg/ml) for 3 hours $\pm$ 5 minutes (37°C , 5% CO_2) and then the formazan crystals were extracted in isopropanol for 2 hours $\pm$ 5 minutes at room temperature. The optical density reading was performed at 540 nm.

The composition of the invention containing PURIFIED WATER F.U. 30.8%, 1,3-PROPANEDIOL (PDO) 41%, VEGETAL GLYCEROL 28%, GRANULAR SODIUM BENZOATE EP-E 211 0.2% (mg, powder), was tested in the aforesaid MTT test, resulting in a treated tissue vitality percentage of about 100%.

Therefore, the base composition of the present invention does not exhibit the cytotoxicity which is typical of compositions for electronic cigarettes based on propylene glycol, thus making the practice of "vaping" much safer.

Panel test with users

To assess whether our liquid is more effective than the current electronic cigarette in delivering nicotine, a test was conducted with regular users. The tests were

designed involving 16 "dual users", ie traditional smokers who also use electronic cigarettes. Since the choice of nicotine concentration is a very subjective parameter, the volunteers were asked to compare the performance of their traditional cigarette with their traditional electronic cigarette and with the composition according to the invention, balancing the nicotine concentration between our liquid and that present in the traditional electronic cigarette.

The composition according to the invention is the same as the previous example.

The conventional composition contains an amount of nicotine ranging from 4 to 12 mg/ml with a preference for the concentration of 8 mg/ml.

The data are shown in the following table I.

Table I - Results of test on regular users

PERCEIVED INTENSITY (1=LITTLE intense; 8=VERY intense)									
	1	2	3	4	5	6	7	8	Average
cigarette						4	3	9	7,3
Conventional e- cigarette composition					4	9	2	1	5,8***
e-cigarette composition of invention					1		12	3	6,9 ns ooo

THROAT SHOT									
(1=little strong; 8=very strong)									
cigarette					2	1	8	5	7,2
Conventional e-cigarette composition						8	7	1	6,45**
e-cigarette composition of invention				1	2	5	7	1	6,2** NS
NICOTINE PERCEPTION SPEED									
(1=very slow; 8=very fast)									
cigarette						1	9	6	7,45
Conventional e-cigarette composition					10	3	2	1	5,3***
e-cigarette composition of invention					2	3	4	7	7,1 ns ooo
LEVEL OF SATISFACTION									
(1=little satisfying; 8=very satisfying)									
cigarette						1	6	9	7,6
Conventional e-cigarette composition					4	7	3	2	5,9***
e-cigarette composition of invention					2	3	8	3	6,8** ooo
Nicotinic contents	4	6	8	9	12				

analyzed (mg)					
No. samples	2	1	5	2	1

Cigarette vs Conventional e-cigarette composition or cigarette vs e-cigarette composition of invention

*** $p < 0,001$ the difference is statistically significant

** $p < 0,01$ the difference is statistically significant

* $p < 0,05$ the difference is statistically significant

ns the two products are equivalent.

Conventional e-cigarette composition vs e-cigarette composition of invention

°° $p < 0,001$ the difference is statistically significant

° $p < 0,01$ the difference is statistically significant

° $p < 0,05$ the difference is statistically significant

NS the two products are equivalent.

The intensity of nicotine is statistically perceived in the same way in the cigarette and in the composition according to the invention and significantly less in conventional compositions.

The throat shot is perceived significantly less both in the conventional composition and in the composition of the invention than in the cigarette. Conventional composition and composition of the invention do not show significant differences.

The rate of perception of nicotine is statistically

perceived in the same way in the cigarette and in the composition of the invention and significantly less in the conventional composition.

The level of satisfaction is significantly higher in the cigarette than in the other two products, but the composition of the invention is significantly better than the conventional composition.

From the above data it therefore appears that the composition of the invention is not only less toxic than conventional compositions for electronic cigarettes, but allows for better availability of nicotine, thus approaching the sensory and general satisfaction performance of a traditional cigarette.

It is apparent that only a few particular embodiments of the present invention have been described, and those skilled in the art will be able to make all the necessary changes thereto for the adaptation to particular applications, without departing from the scope of protection of the present invention.

CLAIMS

1. A composition for inhalation by electronic cigarette that does not contain propylene glycol and that comprises or consists of the following components:

- | | |
|---|-------------------|
| a) water | 25-40% by weight |
| b) 1,3-propanediol | 30-50% by weight |
| c) glycerol | 20-30% by weight |
| d) a preservative | 0.1-5% by weight |
| e) optionally, nicotine | 0.2-6% by weight |
| f) optionally, a flavouring | 0-10% by weight |
| g) optionally, at least
a cyclodextrin | 0.1-5% by weight. |

2. The composition according to claim 1, wherein the preservative is sodium benzoate.

3. The composition according to claim 1 or 2, wherein the flavourings are chosen from fruit, tobacco, mentholated aromas or their mixtures.

4. The composition according to any one of claims 1 to 3, comprising cyclodextrins.

5. The composition according to any one of claims 1 to 4, comprising or consisting of the following components:

- | | |
|--------------------|------------------|
| a) water | 29-33% by weight |
| b) 1,3-propanediol | 38-43% by weight |
| c) glycerol | 22-28% by weight |
| d) a preservative | 0.1-5% by weight |

- e) optionally, nicotine 0.2-6% by weight
- f) optionally, a flavouring 0-10% by weight
- g) optionally, at least
a cyclodextrin 0.1-5% by weight.

6. A kit comprising one or more doses of the composition according to any one of claims 1 to 5 and one or more doses of flavourings.

7. An inhalation device containing one or more doses of the composition according to any one of claims 1 to 5 with or without doses of flavourings.