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(54) **TOBACCO AND/OR TOBACCO IN COMBINATION WITH TOBACCO SUBSTITUTE COMPOSITION FOR USE AS A SNUFF IN THE ORAL CAVITY**

TABAK UND/ODER TABAK IN KOMBINATION MIT TABAKERSATZ ZUSAMMENSETZUNG ZUR VERWENDUNG ALS SCHNUPF IN DER MUNDHÖHLE

TABAC ET/OU SUBSTITUT DE TABAC EN COMBINAISON AVEC DU TABAC S'UTILISANT COMME TABAC A PRISER DANS LA CAVITE BUCCALE

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- **PATENT ABSTRACTS OF JAPAN vol. 1999, no. 06, 31 March 1999 (1999-03-31) & JP 01 108966 A (KOWA DISPLAY:KK), 26 April 1989 (1989-04-26)**

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to a novel composition for the use as snuff in the oral cavity, the composition comprising tobacco and/or tobacco in combination with a tobacco substitute encapsulated in a membrane material comprising one or more membranes at least one of which being water permeable and water-insoluble. A novel composition enables a selective release of e.g. nicotine while it at the same time reduces the release of substances, which normally lead to unwanted side effects. The novel compositions may be used as a healthier alternative to snuff and other tobacco products such as, e.g., cigarettes, cigars and pipe.

[0002] The invention also relates to methods for giving up smoking, reducing nicotine craving, reducing side effects normally related to smoking and snuffing of tobacco as well to a method for the preparation of a composition according to the invention.

BACKGROUND OF THE INVENTION

[0003] The use of tobacco is deeply rooted in a large part of the world population. In the Scandinavian countries and in particular Sweden the use of moist snuff (snus) is very common as an alternative to smoking. Snuff is fermented and milled/grinded tobacco with a relatively large water content (40 - 60 % w/w), normally to be used under the front upper lip of a human being.

[0004] Tobacco itself varies somewhat in nicotine content due to its natural origin. To adjust the nicotine release in moist snuff, various buffer systems may be added, e.g. carbonates. The moist snuff is either packed loosely, as bulk in a box or as single doses in small non-woven bags. A number of the filled and sealed bags are then packed in a box.

[0005] The moist snuff as a single dose has become popular due to the ease of use compared to the bulk product. The popularity of moist snuff is most probably due to its pharmacological nicotine absorption profile. The dose of nicotine and speed of absorption is approximately 10 ng per ml over 10 minutes. Plasma nicotine concentrations rapidly increase within the first few minutes of the use of snuff and reach levels comparable to those obtained from smoking cigarettes within 30 min of use. Measurements of plasma nicotine concentrations after a single day of moist snuff consumption also yielded levels similar to cigarette use.

[0006] The kinetics is slightly slower compared to the kinetics when smoking tobacco, such as e.g. cigarettes and cigars; however, the overall amount of nicotine absorbed is higher when snuff is employed.

[0007] Like the daily use of cigarettes, cigar, pipe and other smoke products, a daily use of snuff burdens the users body with a number of harmful compounds endogenous to tobacco.

[0008] The disadvantage of snuff is the vast number of compounds, more or less harmful to the body, e.g. different tobacco-specific nitrosamines, which are compounds known to cause different diseases such as, e.g., gastro-intestinal disorders and cancer.

[0009] Various tobacco products and/or devices for tobacco products wherein the user achieves the desired effect from nicotine, but at the same time avoids the harmful substances released from the tobacco are already known from the literature.

[0010] In US 4,848,376 an inhalation device is presented where tobacco is used more or less as in a cigarette and the nicotine is liberated due to elevated temperatures, though below the combustion temperature of tobacco.

[0011] US 4,141,369 describes a method of inhaling the nicotine from tobacco without combustion of the tobacco.

[0012] Another way of avoiding the harmful substances contained in tobacco is to substitute tobacco with nicotine.

[0013] In US 4,655,231 an artificial dry snuff containing nicotine is suggested. The snuff, composed of pure nicotine salts and excipients e.g. powdered organic sugars, is intended for the administration to the nasal membranes. This is a medicinal nasal composition not based on natural tobacco.

[0014] Various devices have also be constructed in order to deliver nicotine from a tobacco composition placed in the oral cavity:

[0015] US 5,346,734 describes a perforated latex oral pouch for loose, moist snuff, the pouch serving as a barrier to avoid direct physical contact between the tobacco product and the gum. The pouch has to be filled by the user, cut to fit the mouth cavity of the user and is re-usable.

[0016] US 6,162,516 describes a shield, which also has to be filled with snuff by the user, the shield acting as a barrier to reduce tobacco contact with the sensitive inner cheek lining and gum surfaces while using snuff.

[0017] Both US 5,346,734 and US 6,162,516 do provide the user with a protective device to avoid a direct contact of the tobacco fibers in the snuff with the oral tissues, but no means have been taken in order to avoid or reduce the release of potentially harmful and unwanted substances. Thus, potentially harmful and unwanted substances are still released from the tobacco into the oral cavity.

[0018] None of the above documents has solved the problems concerning eliminating or delaying the release in the

oral cavity of unwanted and harmful substances when using a tobacco containing product as a snuff. Thus, there is still a need for the development of tobacco containing products, which do not deliver unwanted and harmful substances to the body after application.

DISCLOSURE OF THE INVENTION

[0019] Accordingly, the present invention provides a composition wherein the release of nicotine from snuff can be designed freely, even though the release of unwanted and harmful substances from the tobacco is dramatically reduced.

[0020] Thus, the present invention provides a composition for use in the oral cavity comprising tobacco and/or tobacco in combination with a tobacco substitute encapsulated in a membrane material comprising one or more membranes at least one of which being water permeable and water-insoluble.

[0021] The gist of the invention is the employment of a membrane material which makes it possible to deliver nicotine and/or a nicotine derivative, analog, salt, solvate or a mixture thereof in a predetermined manner and - at the same time - has the properties of withholding the substances which are unwanted to such a degree that the side-effects normally observed in connection with the use of snuff in the oral cavity are dramatically reduced.

Tobacco

[0022] The tobacco used in the novel snuff composition according to the invention may be natural tobacco leaves in order to preserve the authentic taste and feeling of tobacco. The tobacco plant belongs to the family *Solanaceae* and the genus *Nicotiana.* More than 60 tobacco species exists, the most commonly used in smoking or snuffing tobacco products being *Nicotiana tabacum* and *Nicotiana rustica.* To manufacture moist snuff, the tobacco, which typically has a content of from about 1% to 8% nicotine, is dried, milled and mixed with a fermentative solution. The mixture is then fermented, typically for 5 days to 4 weeks at elevated temperature. After this the tobacco mass is mixed with a suitable buffer, such as e.g. carbonate, so a pH of about 6 to 8 for the moist snuff mixture is obtained, to enable and enhance the release of nicotine or a derivative thereof from the tobacco. The water content in the final product may lie in the range from about 10 % to about 60 %.

[0023] To the moist snuff additional compounds may be added, such as e.g. sweeteners, aroma substances and other taste additives, detergents and preservative, release modifying agents, and other liquids such as oil, organic solvents and herbal extracts.

[0024] In another embodiment of the invention the natural fermented tobacco may be partly substituted with a tobacco substitute, such as, e.g., nicotine and/or a nicotine derivative, analog, salt, solvate or a mixture thereof selected from the group consisting of nor-nicotine, lobeline, methylanabasine, anabasine, nicotine hydrochloride, nicotine dihydrochloride, nicotine sulphate, nicotine monotartrate, nicotine bitartrate, nicotine salicylate or nicotine zinc chloride monohydrate. To maintain the same feeling of having the moist snuff product in the oral cavity, some additional filler may be added, such as, e.g., non-digestible fibers.

[0025] Whether natural tobacco and/or tobacco in combination with a tobacco substitute are used for the novel snuff composition, the tobacco and/or tobacco substitute may preferably have a content of nicotine and/or a nicotine derivative, analog, salt, solvate or a mixture thereof, from about 0% w/w to about 30% w/w such as, e.g., from about 0.5% w/w to about 25% w/w, from about 0.1% w/w to about 20% w/w, from about 0.1% w/w to about 15% w/w, from about 0.1% w/w to about 10% w/w, from about 0.1% w/w to about 9% w/w or from about 0.1% w/w to about 8% w/w.

Membrane material

[0026] According to the invention, the tobacco and/or tobacco substitute is enclosed in a membrane material. The membrane material may comprise one or more membranes. In the present context the term "membrane" describes a thin polymeric film having natural pores and acting as a selective permeability barrier. The term does not include paper-made material or polymeric materials in which not-naturally occurring openings have been made.

[0027] At least one of the membranes may be water-insoluble to prevent spreading of the snuff in the oral cavity, and to maintain the beneficial properties of the selective membrane material during use, with respect to the withholding of unwanted substances.

[0028] At least one of the membranes may be water permeable in order to allow water to diffuse into the encapsulated tobacco and/or tobacco substitute and to allow e.g. nicotine to diffuse through the polymeric membrane material and thus becoming available for absorption.

[0029] The membranes may have a predominantly hydrophilic or hydrophobic nature. The hydrophilic or hydrophobic nature of the membrane has an effect on the release of substances such as, e.g., nicotine through the membrane, since the flow of substances through the membrane is dependent on the ability of the membrane to hydrate, e.g. create hydro-channels through the membrane. These hydro-channels are a prerequisite for molecular transport when dry polymeric

membranes are used. In general, the flow of hydrophilic substances through a hydrophobic membrane is slower compared to a hydrophilic membrane. This is probably due to less swelling of the hydrophobic membrane pores, i.e. in the hydrophobic membranes nicotine diffusion occurs through well-organized polymeric material and hydrophobic organized water.

[0030] One or more of the membranes used for making the composition may be a synthetic or semi-synthetic membrane. Below is given some examples of natural, synthetic and semi-synthetic hydrophilic and hydrophobic membranes, which may be used in a novel snuff composition according to the invention.

[0031] Examples of membranes are membranes made of cellulose acetate and derivates thereof, carboxymethyl cellulose membranes, polycellulose ester membranes, other cellulose derivatives such as, e.g., ethylcellulose, propylcellulose, polyethylene membranes, polypropylene membranes, polystyrene membranes, polyvinyl chloride membranes, polyvinyl acetate membranes, membranes made of polymers of methacrylates and acrylates, natural rubber membranes, polycarbonate membranes, polyethylene terephthalate membranes, polyester membranes, polyamide membranes and nylon membranes.

[0032] At least the outer membrane in the membrane material enclosing the tobacco and/or tobacco substitute may be made from a biocompatible and physiologically acceptable polymeric material, since the novel snuff composition has to be placed close to or in contact with the mucous membrane in the oral cavity during use.

[0033] Furthermore, at least one of the membranes in a membrane material may be surface treated with e.g. polycarbophils to obtain a bioadhesiveness of the novel snuff composition in the oral cavity.

[0034] The molecular weight cut off of the membrane material used in the novel snuff composition may be varied to obtain a desired release of nicotine and other substances through the membrane material. The molecular weight cut-off of a membrane is defined as the molecular weight of the smallest molecule of which 90 % will be prevented from permeating the membrane. In addition to molecular weight, the exact permeability of a molecule is dependent on the shape, the degree of hydration and the charge of the molecule.

[0035] At least one of the membranes comprising the membrane material may have a molecular weight cut-off from about 500 to about 40,000 such as, e.g., from about 500 to about 5,000, from about 800 to about 4,000, from about 1,000 to about 3,500; or from about 2,000 to about 40,000, from about 3,000 to about 30,000, from about 5,000 to about 25,000, from about 7,500 to about 20,000 or from about 10,000 to about 20,000.

[0036] The release of nicotine and/or other substances through the membrane material is also dependent on the thickness of the membrane materiel. The diffusion process of molecules through the membrane is decreased when the membrane thickness is increased and vice versa. Thus, the thickness of the membrane material may be varied in respect of obtaining a desired release of nicotine and other substances through the membrane material.

[0037] The lower limit for the membrane material thickness is determined by what is possible from a practical point of view, and the upper value is restricted by what will allow a comfortable fit of the novel snuff composition in the oral cavity of the user.

[0038] Accordingly, at least one of the membranes comprising the membrane material may have a thickness of from 2 to about 200 μm such as, e.g., from about 5 to about 100 μm, from about 7.5 to about 50 μm, from about 7.5 to about 40 μm, from about 7.5 to about 35 μm, from about 7.5 to about 30 μm or from about 7.5 to about 25 μm.

Release profiles

[0039] To obtain an effect from the novel snuff composition, nicotine or a nicotine derivative, analog, salt, solvate or a mixture thereof, selected from the group consisting of nor-nicotine, lobeline, methylanabasine, anabasine, nicotine hydrochloride, nicotine dihydrochloride, nicotine sulphate, nicotine monotartrate, nicotine bitartrate, nicotine salicylate or nicotine zinc chloride monohydrate, has to be released from the composition.

[0040] The release profile may be designed with respect to the rate and amount of nicotine and unwanted substances released by the membrane.

[0041] The release of nicotine and/or a derivative, analog, salt, solvate or a mixture thereof from a novel snuff composition may be designed to be released in a sufficient amount and/or a sufficient rate to enable a desired effect and on the other hand be designed to retain substances, which normally give rise to side-effects, such as, e.g., nitrosamines, and/or to release such substances in a substantially low amount and/or at a substantially slow rate.

[0042] As a measure of the selective release of nicotine or a derivative, analog, salt, solvate or a mixture thereof, the Impurity Index- IPI - is introduced.

[0043] The IPI is calculated from the UV-spectra recorded from 200 nm to 900 nm as described in Example 2, and is defined as the ratio of the sum of peak heights other than that of nicotine (i.e. thus including unwanted and harmful substances) to the peak height of nicotine. In other words, a low IPI reflects that a large amount of nicotine is released through the membrane compared to the amount of unwanted substances.

[0044] In a preferred embodiment of the invention the impurity index IPI is at the most 3.0 such as, e.g. at the most 2.75, at the most 2.5, at the most 2.0, at the most 1.75, at the most 1.5, at the most 1.5 or at the most 1.4 when measured after 90 min.

[0045] In one embodiment of the invention the release profile of nicotine and/or a derivative, analog, salt, solvate or a mixture thereof from the invention could e.g., be fast and equivalent to the release of nicotine from the commercially available moist snuff, while maintaining a low IPI value, i.e. limiting the release of unwanted substances.

[0046] Moreover, a composition according to the invention can be designed to release nicotine and/or a derivative, analog, salt, solvate or mixture thereof in a controlled manner such as, e.g., fast (faster than from the reference product employed in the examples herein), relatively fast (i.e. similar or almost similar to the reference product employed in the examples herein), delayed (i.e. with a lag time in which period no nicotine is released followed by a release of nicotine), prolonged or sustained (i.e. a relatively slower release than the reference product to avoid any peak concentration and to obtain a relatively constant plasma concentration of nicotine after application).

[0047] In another embodiment of the invention the release of nicotine or a derivative, analog, salt, solvate or a mixture thereof, may be delayed compared to the commercially available moist snuff, to mimic the effect of nicotine replacement products such as, e.g., patches.

[0048] The release of nicotine or a derivative, analog, salt, solvate or a mixture thereof, may be determined by the release test described in Example 1, but other suitable methods for determining the release of nicotine may also be used, i.e. the embodiments of the invention described below referrer to Example 1 without limiting the relevant release tests to the one described in Example 1.

[0049] The tobacco and/or tobacco in combination with a tobacco substitute composition may be designed so that at least about 50% w/w of the total content of nicotine and/or a derivative, analog, salt, solvate or a mixture thereof is released within at the most 60 min when subject to the release test described in Example 1 below.

[0050] In a further embodiment of the invention the tobacco and/or tobacco substitute composition may be designed so that at the most 25% w/w of the total content of nicotine and/or a derivative, analog, salt, solvate or a mixture thereof is released within at the most 60 min when subject to the release test described in Example 1 below.

[0051] In yet another embodiment the tobacco and/or tobacco substitute composition may be designed so that at least about 50% w/w of the total content of nicotine and/or a derivative, analog, salt, solvate or a mixture thereof is released within at the most 120 min when subject to the release test described in Example 1 below.

[0052] Below follows release profiles for compositions according to the invention. The release profiles are described as %w/w released of total nicotine content as a function of time, measured at 0, 3, 30, 90 and 180 minutes. However, the release profiles according to the invention also includes profiles described by only one or any combination of the values below, i.e. a release profile according to the invention could be defined by e.g. the %w/w release of nicotine at 3 minutes and 90 min, or at 3 and 90 and 180 minutes, or at 90 and 180 minutes or any possible combination of the values shown below.

[0053] A composition according to the invention is suitable designed to release nicotine and/or a derivative, analog, salt, solvate or a mixture thereof from the tobacco or tobacco in combination with the tobacco substitute with the following characteristics:

time (min)	% w/w released of total nicotine content
0	from about 0 to about 20 such as, e.g., from about 0 to about 15 or from about 0 to about 10,
3	from about 0 to about 40 such as, e.g., from about 0 to about 35, from about 0 to about 30, from about 0 to about 25, from about 0 to about 20,
30	from about 2 to about 100, such as, e.g., from about 2 to about 90, from about 2 to about 80, from about 2 to about 70, from about 2 to about 65, from about 2 to about 60, from about 5 to about 60, from about 5 to about 55, from about 7.5 to about 55 or from about 10 to about 50, op til 100
90	from about 10 to about 100 such as, e.g., from about 10 to about 95, from about 15 to about 90, from about 20 to about 90, from about 25 to about 85, from about 30 to about 80, from about 35 to about 80 or from about 40 to about 80,
180	from about 40 to about 100 such as, e.g. from about 45 to about 100, from about 50 to about 100, from about 55 to about 100, from about 60 to about 100, from about 65 to about 100 or from about 70 to about 100,

and the release is determined as described herein in Example 1.

[0054] More specifically, a composition according to the invention releases nicotine and/or a derivative, analog, salt, solvate or a mixture thereof from the tobacco or the tobacco in combination with a tobacco substitute with the following release profile characteristics:

time (min)	% w/w released of total nicotine content
0	from about 0 to about 15

(continued)

time (min)	% w/w released of total nicotine content
3	from about 1 to about 25
30	from about 7.5 to about 55
90	from about 35 to about 80
180	from about 65 to about 100

and the release is determined as described herein in Example 1.

[0055] In a further embodiment, a composition according to the invention releases, nicotine and/or derivative, analog, salt or solvate thereof from the tobacco or the tobacco in combination with a tobacco substitute with the following release profile characteristics:

time (min)	% w/w released of total nicotine content
0	from about 0 to about 10
3	from about 1 to about 20
30	from about 10 to about 50
90	from about 40 to about 90
180	from about 70 to about 100

and the release is determined as described herein in Example 1.

[0056] In a still further embodiment, a composition according to the invention releases nicotine and/or a derivative, analog, salt, solvate or a mixture thereof from the tobacco or the tobacco in combination with a tobacco substitute with the following release profile characteristics:

time (min)	% w/w released of total nicotine content
0	from about 0 to about 10
3	from about 1 to about 20
30	from about 30 to about 50
90	from about 65 to about 90

and the release is determined as described herein in Example 1.

Design of membrane material

[0057] As described above, membrane material properties such as hydrophobicity, hydrophilicity, molecular weight cut-off and membrane thickness may be used in designing a desired release profile for nicotine or a derivative, analog, salt, solvate or mixture thereof.

[0058] In the following are given some examples of how membrane materials can be designed. The examples are for illustrative purposes and are not intended to limit the invention in any way.

[0059] A multi-layer membrane is e.g. designed to contain one membrane material being hydrophilic and a second membrane material being lipophilic. Both membrane components are chosen in such a manner that the membrane material has a molecular cut off large enough for the relatively small nicotine molecule to pass through with ease.

[0060] The amphiphilic nature of nicotine enables it to pass both hydrophilic and hydrophobic materials while a majority of both hydrophilic and lipophilic unwanted and harmful substances are excluded from permeation through the membrane material. Many other combinations of different types of membranes are of course possible and based on the disclosure herein a skilled person will know how to chose different membranes in order to obtain a suitable release.

[0061] Another example of a composition according to the invention is a composition wherein the membrane material is a bi-layer membrane with one membrane being preferentially hydrophilic and one membrane being predominantly hydrophobic. Both membranes possess high permeability to nicotine while maintaining low aqueous pore diffusion. The release profile of nicotine could either be identical to the release profile of original snuff or it could be designed to have a prolonged or sustained release. The unwanted and harmful substances from the tobacco should substantially be maintained inside the membrane.

Shape and size of a composition according to the invention

[0062] A composition according to the invention may attain all possible sizes and shapes, such as, e.g. round, circular, oblong, elliptical, square, rectangular or trapezoidal. The shape and/or size chosen may be such as to allow a comfortable fit in the oral cavity.

[0063] The location in the oral cavity of a composition according to the invention may be centered or to the sides under the upper front lip, centered or to the sides under the lower front lip, under the tongue or in the cheeks.

Other aspects of the invention

[0064] In other aspects, the invention also relates to use of a composition according to the invention as a smoke substitute and it can be used by persons who suffer from nicotine craving or who want to give up or reduce smoking. In such cases, the content of tobacco and/or a tobacco substitute is adjusted to the individual purposes and it is possible to design a kit comprising compositions according to the invention with different concentrations of tobacco and/or a tobacco substitute. Such compositions in a kit could e.g. contain compositions with a decreasing content of tobacco or nicotine.

[0065] In a still further aspect of the invention it relates to a method for preparing a composition according to the invention.

[0066] The details and description relating to the composition aspects apply *mutatis mutandi* to the other aspects of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0067]

Figure 1 shows the release profile from moist tobacco using side-by-side diffusion cells equipped with specific membranes having different physical properties.

Figure 2 shows the impurity index (IPI) for various hydrophilic membranes with different thickness and molecular weight cut-offs. The reference is filter paper.

Figure 3 shows the maximum flux of nicotine as a function of membranes thickness for a hydrophilic membrane with a molecular weight cut-off of 13,000. The reference flux illustrates the flux through filter paper.

[0068] The following examples are intended to illustrate the invention without limiting it thereto.

EXAMPLES

Example 1

Diffusion profiles of hydrophobic membranes and hydrophilic membranes with different physical properties

[0069] Membranes made of regenerated cellulose acetate dialysis tubing with varying MW cut-off together with vinyl and polyethylene membranes with various thicknesses were tested with respect to the diffusion profiles over the membranes of nicotine released from tobacco.

Diffusion chamber experiment

[0070] In a side-by-side diffusion chamber separated by a membrane, 1 g of snuff tobacco (SVENSKT SNUS, GOTHIATEK, General) was placed in an aqueous PBS (phosphate buffered saline according to Ph. Eur.) with a pH of 6.6 on the donor side of the membrane in the diffusion chamber. In the receiver chamber PBS with a pH of 6.6 was placed. The cells of the diffusion chamber were kept at a temperature of 37°C $\pm$ 0.5°C by attachment to a water bath. The temperature control was made in order to simulate the environment of the oral cavity.

[0071] Diffusion profiles were constructed by sampling from the receiver chamber at 0, 3, 30, 60, 90, 120, (110 min for the polyethylene membrane) and 180 min after the start of the diffusion experiment. The concentration of nicotine in the receiver chamber was measured by HPLC, using a C-18, 5μ, 4.5 mm x 15 cm column, employing a mobile phase consisting of 70 % v/v 0.1 M phosphate buffer (pH 4.5), 30 % acetonitrile, and 2.3 g sodium dodecyl sulphate/liter at a flow rate of 1 ml /min and a temperature of 40°C. The sample volume was 10 μl and detection was carried out using a

UV-detector running at 260 nm.

[0072] The membranes used were regenerated cellulose acetate dialysis tubing with varying MW cut-off and vinyl and polyethylene membranes with varying thickness.

[0073] As a reference a piece of filter paper with a average pore size of 8.8 μm, mimicking the commercially used non-woven bag for snuff, was used.

Reference filter paper

[0074] Table I shows a comparison of the release profile of nicotine for a commercial non-woven snuff-bag, and a piece of filter paper used as reference in the experiments. The measurements were performed as described above, and the results are the mean of 2 single runs.

Table I. Comparison of the nicotine release profile for a commercial non-woven filter and a reference paper filter

Filter type	Nicotine released (mg/ml)			
	15 sec.	30 min.	60 min.	90 min.
Reference paper filter	11.5	64.4	92.0	202.4
Commercial non-woven filter	9.4	65.8	90.1	205.5

[0075] The results from Table I show that the reference filter paper exerts no barrier function to the transport of nicotine.

Hydrophobic membranes

[0076] Hydrophobic membranes, e.g. vinyl and polyethylene membranes, show a slower nicotine release profile compared to hydrophilic membranes (see Figure 1). The slower profile is probably due to less swelling of the hydrophobic membrane pores, i.e. in the hydrophobic membranes nicotine diffusion occurs through well-organized polymeric material and hydrophobic organized water rather than through aqueous pores.

[0077] In Table 2 below are given the results from the above-mentioned experiment.

Hydrophilic membranes

[0078] Figure 1 shows that the release of nicotine over a hydrophilic membrane made of regenerated cellulose acetate dialysis tubing is high and close to the nicotine release over the reference filter paper. Figure 1 also shows that the physical properties, i.e. the molecular weight cut-off and thickness of the hydrophilic membrane, affect the permeability of nicotine as stated below.

[0079] A membrane with a relatively small molecular weight cut-off, e.g. a molecular weight cut-off of 3,500, tends to have a sigmoid release profile for nicotine. In other words, a considerable lag time is expected before the nicotine starts to permeate the membrane, even though the size of a nicotine molecule is significantly smaller than the molecular weight cut-off of 3,500.

[0080] However, a membrane with a higher molecular weight cut-off, e.g. a molecular weight cut-off of 13,000, seems to have a release profile for nicotine that is very close to the release profile for nicotine of the reference filter paper.

[0081] This difference may be due to a much lower aqueous mobility of nicotine in the membrane with a molecular weight cut-off of 3,500, compared to the membrane with a molecular weight cut-off of 13,000.

[0082] Figure 1 also shows that when the thickness of a membrane increases, then the flux of nicotine through the membrane decreases.

[0083] Example 1 shows that it is possible to design a polymeric membrane which gives rise to a release profile of nicotine from moist tobacco through the membrane very similar to the release profile through a commercial non-woven snuff-bag, i.e. with respect to the shape of the profile and the individual release data (time, percentage released). Especially, it seems that a hydrophilic membrane material is suitable. Furthermore, the release profile is dependent of the molecular weight cut-off of the membrane, the thickness of the membrane and of the membrane material itself.

[0084] Example 1 also shows that some hydrophobic membranes, e.g. vinyl and polyethylene membranes, have a slower nicotine release profile compared to the hydrophilic membranes.

[0085] All these observations make it possible to design membranes, which enable a specific release of nicotine, i.e. it is possible to design membranes having desired release characteristics e.g. a quick or a slow release of nicotine

dependent on the purpose of the composition. In other words, the specific features of a membrane or a membrane material can be used to design a controlled and well-defined release profile for the release of nicotine from a composition according to the invention.

Table 2: Release of nicotine from membranes of various kinds, thicknesses and pore sizes

Membrane	Release of nicotine (%)					
	0 min	3 min	30 min	90 min	120 min	180 min
Reference filter (original)	4.7	18.7	46.5	80.8	88.8	100
23 μm cellulose membrane 13,000 MW cut-off	2.4	4.1	36.6	73.2	83.7	100
46 μm cellulose membrane 13,000 MW cut-off	1.6	2.4	33.3	69.1	79.2	100
93 μm cellulose membrane 13,000 MW cut-off	0	0	17.2	43.9	49.0	69.7
25 μm cellulose membrane 3,500 MW cut-off	0.9	2.7	11.6	67.0	75.9	100
50 μm cellulose membrane 3,500 MW cut-off	0.9	1.7	4.3	49.9	56.8	80.0
20 μm Polyetylene	0	0	3.0	--	22*	--
* Measured after 110 min						

Example 2

Selectivity of the release of tobacco components over membranes with different properties

[0086] Membranes made from regenerated cellulose acetate dialysis tubing with varying thickness and molecular weight cut-off were tested for their selectivity in transporting nicotine across the membrane, while unwanted and potentially harmful substances are retained in the tobacco.

[0087] To examine the selectivity of the membranes, an experimental set-up as described in Example I was used.

[0088] As membranes were used regenerated cellulose acetate with molecular weight cut-off of 3,500 and a thickness of 25.2 μm or a molecular weight cut-off of 13,000 and a thickness of 23.2 μm or 46.4 μm. Samples were withdrawn at 3, 30 and 90 minutes after the start of the experiment and an UV spectrum from 200 nm to 900 nm was recorded for each sample.

[0089] As previous described, the Impurity Index - lPI - was introduced as a measure for the selective release of nicotine. The IPI is calculated from the UV-spectra recorded from 200 nm to 900 nm, and is defined as the ratio of the sum of peak heights other than that of nicotine (i.e. thus including unwanted and harmful substances) to the peak height of nicotine. All measurements are performed in the receiver chamber, i.e. after permeation through the membrane in question. The IPI is measured 3, 30 and 90 min after start of the experiment, cf. above. In those cases where any additionally substances are added to the tobacco composition such as, e.g., sweeteners, flavors, detergents, buffers, etc. the peak heights of these are normally not included when calculating the sum of peak height as described above.

[0090] As mentioned before, a low IPI reflects that a large amount of nicotine is released through the membrane compared to the amount of unwanted substances. Table 3 shows IPI values calculated for the reference filter paper and for hydrophilic membranes with different molecular weight cut-off and different thickness.

Table 3: Impurity index (IPI) calculated for the reference filter paper membrane and hydrophilic regenerated cellulose acetate membranes with different physical properties

Time (min)	Impurity index (IPI)			
	Membrane 1 Thick: 25.2 μm MWCO 3,500	*Membrane 2* Thick: 23.2 μm MWCO 13,000	*Membrane 3* Thick 46.4 μm MWCO 13,000	Reference
3	0.9	0.75	1.05	1.64
30	1.17	1.24	1.17	2.91
90	1.26	1.35	1.25	3.35
IPI = Σ Peak height other substances/ Σ Peak height nicotine MWCO = molecular weight cut-off				

[0091] The results in Table 3 show that the amount of unwanted substances can be decreased almost three times when a cellulose membrane with a thickness and a molecular weight cut-off in the range described in Table 3 is used compared to the reference filter paper.

[0092] As shown in Figure 1, the decrease in IPI is not merely a result of a decrease in the overall release rate. Accordingly, the release profiles relating to nicotine and employing cellulose membranes with a molecular weight cut-off of 13,000 are only a few percent lower than the release profile for the reference filter paper. Thus, employment of such membranes enables a release, which permits release of wanted substances (i.e. nicotine) while retaining unwanted substances.

[0093] The results from Table 3 and Fig. 1 indicate that the release rate of unwanted substances increases with decreasing membrane thickness. However, it is important to note that such an increase seems to correspond to the increase in the release rate of nicotine, i.e., a decrease in membrane thickness will not lead to a more pronounced release of unwanted substances. In other words, the IPI value is not increasing when the thickness of the membrane with a molecular weight cut-off of 13,000 is decreased from 46.4 μm to 23.2 *μm.*

Example 3

Optimization of membrane properties with respect to molecular weight cut-off, thickness and low IPI values

[0094] Example 2 shows that no significant loss in membrane selectivity is observed as the membrane thickness is being decreased. Therefore, further studies to investigate the relationship between membrane thickness, molecular weight cut-off of the membrane and amount of nicotine transferred over the membrane were performed by analyzing selected data from Example 1.

[0095] From Figure 1, the maximum slope for each release profile has been deduced. The maximum slope, i.e. percentage nicotine release per time unit, dR/dt represents the maximum flux of nicotine through the membranes (see Table 4).

Table 4. Values for the maximum flux (% nicotine released per time unit, dR/dt) and lag time for different thicknesses of membranes with cut off 3500 Mw, 13000 Mw and reference filter

Molecular weight cut-off	Thickness (μm)	Lag time (min)	Maximum flux of nicotine (dR/dt)
∞ (reference pouch)		0	1.250
13,000 MW CO membrane	23.2	0	1.205
	46.4	0	1.144
	92.8	0	0.637
3,500 MW CO membrane	25.2	≈50	1.250
	50.4	≈50	1.204

[0096] Figure 3 shows a plot of the maximum flux as a function of membrane thickness for the cellulose membrane with a molecular weight cut-off of 13,000. The Figure shows that the flux of nicotine through a membrane is approaching the flux through a reference filter paper, which practically has no barrier to the nicotine diffusion, at a membrane thickness of about 10 μm.

[0097] A hydrophilic membrane with a molecular cut off about 13,000 does not seem to give rise to any boundary layer/membrane effects or any major diffusion limitations for nicotine. A thickness of approx.10 μm will give a release profile equal to the original commercially available non-woven moist snuff pouches.

Example 4

Studies of nicotine uptake in humans from a novel snuff composition

[0098] The sensation of nicotine uptake in humans when using commercially available bag-snuff compared to a novel snuff composition according to the invention was studied.

[0099] In the study, the uptake of nicotine from 1 g of snuff (SVENSKT SNUS, GOTHIATEK, General) in original non-woven pouches was compared to the uptake of nicotine from 1 g of snuff contained in a regenerated cellulose membrane with a molecular weight cut-off of 13,000 and a thickness of 23.2 μm.

[0100] The study was performed with human volunteers who were not snuff users.

[0101] Each individual placed a portion of snuff under the upper lip, and they scored their observations concerning the sensation of taking up nicotine into the blood stream within certain time intervals.

[0102] The sensation of taking up nicotine into the blood stream from the oral cavity was scored using a scale rating from zero to five, with zero indicating no feeling and 5 indicating a very strong feeling of uptake, leading to dizziness and nausea.

[0103] The results from the study of nicotine uptake are shown in Table 5.

Table 5. Sensation of nicotine uptake from commercially available bag-snuff and from a snuff composition according to the invention

Subject	Commercially available bag snuff							Moist snuff placed in a membrane with MW CO 13,000						
	Time (min)													
	0	2	4	6	8	10		0	2	4	6	8	12	16
Volunteer #1	0	0	2	3	5	5		0	0	1	2	3	4	5
Volunteer #2	0	0	1	4	5	5		0	0	1	3	4	4	5
Volunteer #3	0	0	1	3	4	5		0	0	1	2	3	4	4

[0104] It is evident from the results shown in Table 5, that the novel snuff composition gives rise to a nicotine effect in the volunteers. Four minutes after the commercially available bag snuff or the novel snuff composition was placed in the oral cavity, two of the volunteers felt a nicotine effect, which they gave a scoring of one. One of the volunteers felt an one-degree higher effect from the commercially available bag snuff compared to the novel snuff composition

[0105] The results also show that the effect of nicotine uptake from the novel snuff composition is slightly delayed compared to the sensation of nicotine uptake from the commercially available bag snuff. When using the commercially available bag snuff, the volunteers feel an effect rated 5 after 8 to 10 minutes. When using the novel snuff composition the volunteers feel the maximum effect between 12 to 16 minutes.

Claims

1. A composition for use in the oral cavity comprising a material selected from the group consisting of tobacco and tobacco in combination with a tobacco substitute, the material being encapsulated in a membrane material comprising one or more membranes at least one of which being water permeable and water-insoluble, and wherein the impurity index of the composition - when determined as described herein - is at the most 3.0 such as, e.g., at the most 2.75, at the most 2.5, at the most 2.0, at the most 1.75, at the most 1.5, at the most 1.5 or at the most 1.4 when measured after 90 min.

2. A composition according to claim 1 for use as snuff.

3. A composition according to claim 1 or 2, wherein the composition is not in the form of a chewing gum.

4. A composition according to any of the preceding claims, wherein at least one membrane is a synthetic or semi-synthetic membrane.

5. A composition according to any of the preceding claims, wherein at least one membrane is made from natural rubber.

6. A composition according to any of the preceding claims, wherein at least one membrane is a biocompatible membrane.

7. A composition according to any of the preceding claims, wherein the membrane is of a polymeric material such as one selected from the group consisting of cellulose acetate and derivates thereof, carboxymethyl cellulose, polycellulose esters, other cellulose derivatives such as, e.g., ethylcellulose, propylcellulose, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polyvinyl acetate, polymers of methacrylates and acrylates, natural rubber, polycarbonates, polyethylene terephthalate, polyesters, polyamides and nylon.

8. A composition according to any of the preceding claims, wherein at least one of the membranes has predominantly hydrophilic character.

9. A composition according to any of the preceding claims, wherein at least one of the membranes has predominantly hydrophobic character.

10. A composition according to any of the preceding claims, wherein nicotine and/or a nicotine derivative, analog, salt, solvate or a mixture thereof is released from the tobacco or the tobacco substitute.

11. A composition according to claim 10, wherein the release is a controlled release.

12. A composition according to claim 10 or 11, wherein the nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof is selected from the group consisting of nor-nicotine, lobeline, methylanabasine, anabasine, nicotine hydrochloride, nicotine dihydrochloride, nicotine sulphate, nicotine monotartrate, nicotine bitartrate, nicotine salicylate or nicotine zinc chloride monohydrate.

13. A composition according to any of the preceding claims, which i) is designed to release nicotine and/or a nicotine derivative, analog, salt, solvate or a mixture thereof in a sufficient amount and/or at a sufficient rate to enable a desired effect and ii) is designed to retain substances, which normally give rise to side-effects, and/or to release such substances in a substantially low amount and/or at a substantially slow rate.

14. A composition according to any of the preceding claims, Wherein at least one of the membranes comprising the membrane material has a molecular weight cut-off of from about 500 to about 40,000 such as, e.g., from about 500 to about 5,000, from about 800 to about 4,000, from about 1,000 to about 3,500, or from about 2,000 to about 40,000, from about 3,000 to about 30,000, from about 5,000 to about 25.000, from about 7,500 to about 20,000 or from about 10,000 to about 20,000.

15. A composition according to any of the preceding claims, wherein at least one of the membranes comprising the membrane material has a thickness of from about 2 to about 200 μm such as, e.g., from about 5 to about 100 μm, from about 7.5 to about 50 μm, from about 7.5 to about 40 μm, from about 7.5 to about 35 μm, from about 7.5 to about 30 μm or from about 7.5 to about 25 μm.

16. A composition according to any of the preceding claims, wherein at least about 50% w/w of the total content of nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof is released within at the most 60 min when subject to the release test described herein.

17. A composition according to any of claims 1-15, wherein at the most 25% w/w of the total content of nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof is released within at the most 60 min when subject to the release test described herein.

18. A composition according to any of claims 1-15 or 17, wherein at least about 50% w/w of the total content of nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof Is released within at the most 120 min when subject to the release test described herein.

19. A composition according to any of the preceding claims, wherein the release of nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof from the tobacco or the tobacco substitute has the following characteristics:

time (min)	% w/w released of total nicotine content
0	from about 0 to about 20 such as, e.g., from about 0 to about 15 or from about 0 to about 10
3	from about 0.5 to about 40 such as e.g., from about 0.5 to about 35, from about 0.5 to about 30, from about 1 to about 25 or from about 1 to about 20

(continued)

time (min)	% w/w released of total nicotine content
30	from about 2 to about 65 such as, e.g., from about 2 to about 60, from about 5 to about 60, from about 5 to about 55, from about 7.5 to about 55 or from about 10 to about 50
90	from about 10 to about 100 such as, e.g., from about 10 to about 95, from about 15 to about 90. from about 20 to about 90, from about 25 to about 85, from about 30 to about 80, from about 35 to about 80 or from about 40 to about 80
180	from about 40 to about 100 such as, e.g., from about 45 to about 100, from about 50 to about 100, from about 55 to about 100, from about 60 to about 100, from about 65 to about 100 or from about 70 to about 100

and the release is determined as described herein.

20. A composition according to any of the preceding claims, wherein the release of nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof from the tobacco or the tobacco substitute has the following characteristics:

time (min)	% w/w released of total nicotine content
0	from about 0 to about 15
3	from about 1 to about 25
30	from about 7.5 to about 55
90	from about 35 to about 80
180	from about 65 to about 100

and the release is determined as described herein.

21. A composition according to any of the preceding claims, wherein the release of nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof from the tobacco or the tobacco substitute has the following characteristics:

time (min)	% w/w released of total nicotine content
0	from about 0 to about 10
3	from about 1 to about 20
30	from about 10 to about 50
90	from about 40 to about 90
180	from about 70 to about 100

and the release is determined as described herein.

22. A composition according to any of the preceding claims, wherein the release of nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof from the tobacco or the tobacco substitute has the following characteristics:

time (min)	% w/w released of total nicotine content
0	from about 0 to about 10
3	from about 1 to about 20
30	from about 30 to about 50
90	from about 65 to about 90

and the release is determined as described herein in.

23. A composition according to any of the preceding claims wherein the tobacco is processed from the leafs of the plant family *Solanaceae* and the genus *Nicotiana,* such as, e.g., *Nicotiana tabacum* and *Nicotiana rustica.*

24. A composition according to any of the preceding claims comprising nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof as claimed in claim 12 together with tobacco in the form of snuff tobacco and/or a suitable filler substance.

25. A composition according to any of the preceding claims wherein the composition further comprises sweeteners, aromas, taste additives, detergents, pH adjusting substances, preservatives, buffers, release modifying agents and/or fillers.

26. A composition according to any of the preceding claims wherein the composition further comprises chemical compounds that enables and enhances the release of nicotine from tobacco such as, e.g., pH regulating buffers, e.g. carbonates buffers oil, organic solvents and herbal extracts.

27. A composition according to any of the preceding claims, wherein the tobacco or tobacco substitute contains nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof in an concentration of about from 0% w/w to about 30% w/w such as, e.g., from about 0.5% w/w to about 25% w/w, from about 0.1% w/w to about 20% w/w, from about 0.1% w/w to about 15% w/w, from about 0.1% w/w to about 10% w/w, from about 0.1% w/w to about 9% w/w or from about 0.1% w/w to about 8% w/w.

28. A composition according to any of the preceding claims, wherein the membrane material is composed of at least two different kinds of membranes with respect to e.g. thickness, molecular weight cut-off, hydrophilic/hydrophobic nature and water permeability.

29. A composition according to any of the preceding claims, wherein the composition has a size and/or shape, which is suitable for application under the upper lip of a human.

30. A composition according to any of the preceding claims containing a mixture of tobacco and a tobacco substitute.

31. A composition according to any of the preceding claims for use as a smoke substitute.

32. A composition according to claim 30 or 31 for use in reducing nicotine craving and/or nicotine abstinence.

33. A method for controlling the release of nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof from tobacco and/or tobacco substitute in the oral cavity, the method comprising encapsulating a material selected from the group consisting of tobacco and tobacco in combination with a tobacco substitute in a membrane material comprising one or more membranes at least one of which being water permeable and water-insoluble so that nicotine and/or nicotine derivative, analog, salt, solvate or a mixture thereof is released in a sufficient amount and/or at a sufficient rate to i) enable a desired effect and ii) retain substances, which normally give rise to side-effects, and/or release such substances in a substantially low amount and/or at a substantially slow rate.

34. A method for delivering nicotine and/or derivative, analog, salt or solvate thereof to a person in need thereof, the method comprising applying a composition according to any of claims 1-32 to the oral cavity.

35. A method for giving up smoking, the method comprising applying a composition according to any of claims 1-32 to the oral cavity.

36. Use of a composition according to any of claims 1-32 in the manufacture of a medicament for reducing nicotine craving, by applying said composition a composition according to any of claims 1-32 to the oral cavity.

37. Use of a composition according to any of claims 1-32 in the manufacture of a medicament for reducing side effects related to smoking and/or snuffing tobacco, by applying said composition to the oral cavity.

38. Use of a composition according to any of claims 1-32 as an alternative to and/or substitute for smoking tobacco.

39. A method for the preparation of a composition according to any of claims 1-32, the method comprising encapsulating tobacco and/or a tobacco substitute in a membrane material comprising one or more membranes at least one of which being a water permeable and a water-insoluble membrane.

Patentansprüche

1. Zusammensetzung zur Verwendung in der Mundhöhle, umfassend ein Material, das aus der Gruppe ausgewählt ist, die aus Tabak und Tabak in Kombination mit einem Tabakersatz besteht, wobei das Material in einem Mem-

branmaterial eingekapselt ist, das eine oder mehrere Membranen umfasst, von denen wenigstens eine wasserdurchlässig und wasserunlöslich ist, und wobei der Verunreinigungsindex der Zusammensetzung, wenn man ihn gemäß der vorliegenden Beschreibung bestimmt, höchstens 3,0 beträgt, wie zum Beispiel höchstens 2,75, höchstens 2,5, höchstens 2,0, höchstens 1,75, höchstens 1,5, höchstens 1,5 oder höchstens 1,4, wenn nach 90 min gemessen wird.

2. Zusammensetzung gemäß Anspruch 1 zur Verwendung als Schnupfmittel.

3. Zusammensetzung gemäß Anspruch 1 oder 2, wobei die Zusammensetzung nicht in Form eines Kaugummis vorliegt.

4. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei wenigstens eine Membran eine synthetische oder halbsynthetische Membran ist.

5. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei wenigstens eine Membran aus Naturkautschuk besteht.

6. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei wenigstens eine Membran eine biologisch verträgliche Membran ist.

7. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei die Membran aus einem polymeren Material besteht, wie einem, das aus der Gruppe ausgewählt ist, die aus Celluloseacetat und Derivaten davon, Carboxymethylcellulose, Polycelluloseestern, anderen Cellulosederivaten, wie zum Beispiel Ethylcellulose, Propylcellulose, Polyethylen, Polypropylen, Polystyrol, Polyvinylchlorid, Polyvinylacetal, Polymeren von Methacrylaten und Acrylaten, Naturkautschuk, Polycarbonaten, Polyethylenterephthalat, Polyestern, Polyamiden und Nylon besteht.

8. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei wenigstens eine der Membranen vorwiegend hydrophilen Charakter hat.

9. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei wenigstens eine der Membranen vorwiegend hydrophoben Charakter hat.

10. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei aus dem Tabak oder Tabakersatz Nicotin und/oder ein Nicotinderivat, -analogon, -salz, -solvat oder Gemisch davon freigesetzt wird.

11. Zusammensetzung gemäß Anspruch 10, wobei die Freisetzung eine kontrollierte Freisetzung ist.

12. Zusammensetzung gemäß Anspruch 10 oder 11, wobei das Nicotin und/oder Nicotinderivat, -analogon, -salz, -solvat oder Gemisch davon aus der Gruppe ausgewählt ist, die aus Nornicotin, Lobelin, Methylanabasin, Anabasin, Nicotin-Hydrochlorid, Nicotin-Dihydrochlorid, Nicotinsulfat, Nicotinmonotartrat, Nicotinhydrogentartrat, Nicotinsalicylat oder Nicotinzinkchlorid-Monohydrat besteht.

13. Zusammensetzung gemäß einem der vorstehenden Ansprüche, die i) Nicotin und/oder ein Nicotinderivat, -analogon, -salz, -solvat oder Gemisch davon in einer ausreichenden Menge und/oder mit einer ausreichenden Geschwindigkeit freisetzen soll, um eine gewünschte Wirkung zu ermöglichen, und ii) Substanzen, die normalerweise zu Nebenwirkungen führen, zurückhalten und/oder solche Substanzen in einer sehr geringen Menge und/oder mit einer sehr niedrigen Geschwindigkeit freisetzen soll.

14. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei wenigstens eine der Membranen, die das Membranmaterial umfassen, eine Molekulargewichtsschwelle von etwa 500 bis etwa 40 000, wie zum Beispiel etwa 500 bis etwa 5000, etwa 800 bis etwa 4000, etwa 1000 bis etwa 3500 oder etwa 2000 bis etwa 40 000, etwa 3000 bis etwa 30 000, etwa 5000 bis etwa 25000, etwa 7500 bis etwa 20 000 oder etwa 10 000 bis etwa 20 000, aufweist.

15. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei wenigstens eine der Membranen, die das Membranmaterial umfassen, eine Dicke von etwa 2 bis etwa 200 μm, wie zum Beispiel etwa 5 bis etwa 100 μm, etwa 7,5 bis etwa 50 μm, etwa 7,5 bis etwa 40 μm, etwa 7,5 bis etwa 35 μm, etwa 7,5 bis etwa 30 μm oder etwa 7,5 bis etwa 25 μm, aufweist.

16. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei wenigstens etwa 50 Gew.-% des Gesamt-

gehalts an Nicotin und/oder Nicotinderivat, -analogon, -salz, -solvat oder Gemisch davon innerhalb von höchstens 60 min freigesetzt werden, wenn gemäß dem hier beschriebenen Freisetzungstest getestet wird.

17. Zusammensetzung gemäß einem der Ansprüche 1 bis 15, wobei höchstens 25 Gew.-% des Gesamtgehalts an Nicotin und/oder Nicotinderivat, - analogon, -salz, -solvat oder Gemisch davon innerhalb von höchstens 60 min freigesetzt werden, wenn gemäß dem hier beschriebenen Freisetzungstest getestet wird.

18. Zusammensetzung gemäß einem der Ansprüche 1 bis 15 oder 17, wobei wenigstens etwa 50 Gew.-% des Gesamtgehalts an Nicotin und/oder Nicotinderivat,- analogon, -salz, -solvat oder Gemisch davon innerhalb von höchstens 120 min freigesetzt werden, wenn gemäß dem hier beschriebenen Freisetzungstest getestet wird.

19. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei die Freisetzung von Nicotin und/oder Nicotinderivat, -analogon, -salz, -solvat oder Gemisch davon aus dem Tabak oder Tabakersatz die folgenden Merkmale aufweist:

Zeit (min)	Gew.-% des Gesamtnicotingehalts freigesetzt
0	etwa 0 bis etwa 20, wie zum Beispiel etwa 0 bis etwa 15 oder etwa 0 bis etwa 10;
3	etwa 0,5 bis etwa 40, wie zum Beispiel etwa 0,5 bis etwa 35, etwa 0,5 bis etwa 30, etwa 1 bis etwa 25 oder etwa 1 bis etwa 20;
30	etwa 2 bis etwa 65, wie zum Beispiel etwa 2 bis etwa 60, etwa 5 bis etwa 60, etwa 5 bis etwa 55, etwa 7,5 bis etwa 65 oder etwa 10 bis etwa 50;
90	etwa 10 bis etwa 100, wie zum Beispiel etwa 10 bis etwa 95, etwa 15 bis etwa 90, etwa 20 bis etwa 90, etwa 25 bis etwa 85, etwa 30 bis etwa 80, etwa 35 bis etwa 80 oder etwa 40 bis etwa 80;
180	etwa 40 bis etwa 100, wie zum Beispiel etwa 45 bis etwa 100, etwa 50 bis etwa 100, etwa 55 bis etwa 100, etwa 60 bis etwa 100, etwa 65 bis etwa 100 oder etwa 70 bis etwa 100;

und die Freisetzung so bestimmt wird, wie es hier beschrieben ist.

20. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei die Freisetzung von Nicotin und/oder Nicotinderivat, -analogon, -salz, -solvat oder Gemisch davon aus dem Tabak oder Tabakersatz die folgenden Merkmale aufweist:

Zeit (min)	Gew.-% des Gesamtnicotingehalts freigesetzt
0	etwa 0 bis etwa 15;
3	etwa 1 bis etwa 25;
30	etwa 7,5 bis etwa 55;
90	etwa 35 bis etwa 80;
180	etwa 65 bis etwa 100;

und die Freisetzung so bestimmt wird, wie es hier beschrieben ist.

21. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei die Freisetzung von Nicotin und/oder Nicotinderivat, -analogon, -salz, -solvat oder Gemisch davon aus dem Tabak oder Tabakersatz die folgenden Merkmale aufweist:

Zeit (min)	Gew.-% des Gesamtnicotingehalts freigesetzt
0	etwa 0 bis etwa 10;
3	etwa 1 bis etwa 20;
30	etwa 10 bis etwa 50;
90	etwa 40 bis etwa 90;
180	etwa 70 bis etwa 100;

und die Freisetzung so bestimmt wird, wie es hier beschrieben ist.

22. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei die Freisetzung von Nicotin und/oder Nico-

tinderivat, -analogon, -salz, -solvat oder Gemisch davon aus dem Tabak oder Tabakersatz die folgenden Merkmale aufweist:

Zeit (min)	Gew.-% des Gesamtnicotingehalts freigesetzt
0	etwa 0 bis etwa 10;
3	etwa 1 bis etwa 20;
30	etwa 30 bis etwa 50;
90	etwa 65 bis etwa 90;

und die Freisetzung so bestimmt wird, wie es hier beschrieben ist.

23. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei der Tabak aus den Blättern der Pflanzenfamilie Solanaceae und der Gattung *Nicotiana,* wie zum Beispiel *Nicotiana tabacum* und *Nicotiana rustica,* verarbeitet wird.

24. Zusammensetzung gemäß einem der vorstehenden Ansprüche, die Nicotin und/oder ein Nicotinderivat, -analogon, -salz, -solvat oder ein Gemisch davon gemäß Anspruch 12 zusammen mit Tabak in Form von Schnupftabak und/oder einer geeigneten Füllsubstanz umfasst.

25. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei die Zusammensetzung weiterhin Süßungsmittel, Aromen, Geschmacksadditive, Detergentien, pH-Regulatoren, Konservierungsmittel, Puffer, Freisetzungsmodifikatoren und/oder Füllstoffe umfasst.

26. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei die Zusammensetzung weiterhin chemische Verbindungen umfasst, die die Freisetzung von Nicotin aus Tabak ermöglichen und verstärken, wie zum Beispiel pH-Regulatoren, zum Beispiel Carbonate, Puffer, Öl, organische Lösungsmittel und Kräuterextrakte umfasst.

27. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei der Tabak oder Tabakersatz Nicotin und/oder ein Nicotinderivat, -analogon, -salz, -solvat oder Gemisch davon in einer Konzentration von etwa 0 Gew.-% bis etwa 30 Gew.-%, wie zum Beispiel etwa 0,5 bis etwa 25 Gew.-%, etwa 0,1 bis etwa 20 Gew.-%, etwa 0,1 bis etwa 15 Gew.-%, etwa 0,1 bis etwa 10 Gew.-%, etwa 0,1 bis etwa 9 Gew.-% oder etwa 0,1 bis etwa 8 Gew.-%, enthält.

28. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei das Membranmaterial aus wenigstens zwei verschiedenen Arten von Membranen besteht, zum Beispiel in Bezug auf die Dicke, Molekulargewichtsschwelle, hydrophile/hydrophobe Natur und Wasserdurchlässigkeit.

29. Zusammensetzung gemäß einem der vorstehenden Ansprüche, wobei die Zusammensetzung eine Größe und/oder Form hat, die für die Anwendung unter der Oberlippe eines Menschen geeignet ist.

30. Zusammensetzung gemäß einem der vorstehenden Ansprüche, die ein Gemisch aus Tabak und einem Tabakersatz enthält.

31. Zusammensetzung gemäß einem der vorstehenden Ansprüche zur Verwendung als Rauchersatz.

32. Zusammensetzung gemäß Anspruch 30 oder 31 zur Verwendung zum Reduzieren des Nicotin-Craving und/oder der Nicotinabstinenz.

33. Verfahren zum Steuern der Freisetzung von Nicotin und/oder einem Nicotinderivat, -analogon, -salz, -solvat oder Gemisch davon aus Tabak und/oder Tabakersatz in der Mundhöhle, wobei das Verfahren das Einkapseln eines Materials, das aus der Gruppe ausgewählt ist, die aus Tabak und Tabak in Kombination mit einem Tabakersatz besteht, in einem Membranmaterial umfasst, das eine oder mehrere Membranen umfasst, von denen wenigstens eine wasserdurchlässig und wasserunlöslich ist, so dass Nicotin und/oder ein Nicotinderivat, -analogon, -salz, -solvat oder Gemisch davon in einer ausreichenden Menge und/oder mit einer ausreichenden Geschwindigkeit freigesetzt werden soll, um i) eine gewünschte Wirkung zu ermöglichen, und ii) Substanzen, die normalerweise zu Nebenwirkungen führen, zurückgehalten und/oder solche Substanzen in einer sehr geringen Menge und/oder mit einer sehr niedrigen Geschwindigkeit freigesetzt werden.

34. Verfahren zur Abgabe von Nicotin und/oder einem Derivat, Analogon, Salz oder Solvat davon an eine Person, die dessen bedarf, wobei das Verfahren das Anwenden einer Zusammensetzung gemäß einem der Ansprüche 1 bis 32 in der Mundhöhle umfasst.

35. Verfahren zum Aufhören mit dem Rauchen, wobei das Verfahren das Anwenden einer Zusammensetzung gemäß einem der Ansprüche 1 bis 32 in der Mundhöhle umfasst.

36. Verwendung einer Zusammensetzung gemäß einem der Ansprüche 1 bis 32 bei der Herstellung eines Medikaments zum Reduzieren des Nicotin-Craving durch Anwenden der Zusammensetzung in der Mundhöhle.

37. Verwendung einer Zusammensetzung gemäß einem der Ansprüche 1 bis 32 bei der Herstellung eines Medikaments zum Reduzieren von Nebenwirkungen, die mit dem Rauchen und/oder Schnupfen von Tabak verbunden sind, durch Anwenden der Zusammensetzung in der Mundhöhle.

38. Verwendung einer Zusammensetzung gemäß einem der Ansprüche 1 bis 32 als Alternative zu und/oder Ersatz des Tabakrauchens.

39. Verfahren zur Herstellung einer Zusammensetzung gemäß einem der Ansprüche 1 bis 32, wobei das Verfahren das Einkapseln von Tabak und/oder Tabakersatz in einem Membranmaterial umfasst, das eine oder mehrere Membranen umfasst, von denen wenigstens eine wasserdurchlässig und wasserunlöslich ist.

Revendications

1. Composition destinée à être utilisée dans la cavité orale, comprenant un matériau choisi dans l'ensemble constitué par le tabac et le tabac en combinaison avec un substitut du tabac, le matériau étant encapsulé dans un matériau de membrane comprenant une ou plusieurs membranes, au moins l'une de celles-ci étant perméable à l'eau et insoluble dans l'eau, et dans laquelle l'indice d'impureté de la composition - quand il est déterminé comme décrit ici - est d'au plus 3,0, comme par exemple d'au plus 2,75, d'au plus 2,5, d'au plus 2,0, d'au plus 1,75, d'au plus 1,5, d'au plus 1,5 ou d'au plus 1,4 quand il est mesuré après 90 minutes.

2. Composition selon la revendication 1, pour une utilisation sous la forme d'une prise.

3. Composition selon la revendication 1 ou 2, laquelle composition n'est pas sous la forme d'une gomme à mâcher.

4. Composition selon l'une quelconque des revendications précédentes, dans laquelle au moins une membrane est une membrane synthétique ou semi-synthétique.

5. Composition selon l'une quelconque des revendications précédentes, dans laquelle au moins une membrane est faite en caoutchouc naturel.

6. Composition selon l'une quelconque des revendications précédentes, dans laquelle au moins une membrane est une membrane biocompatible.

7. Composition selon l'une quelconque des revendications précédentes, dans laquelle la membrane est en un matériau polymère par exemple choisi dans l'ensemble constitué par l'acétate de cellulose et ses dérivés, la carboxyméthylcellulose, les polyesters cellulosiques, d'autres dérivés de cellulose comme par exemple l'éthylcellulose, la propylcellulose, le polyéthylène, le polypropylène, le polystyrène, le poly(chlorure de vinyle), le poly(acétate de vinyle), les polymères de méthacrylates et d'acrylates, le caoutchouc naturel, les polycarbonates, le poly(téréphtalate d'éthylène), les polyesters, les polyamides et le nylon.

8. Composition selon l'une quelconque des revendications précédentes, dans laquelle au moins l'une des membranes a un caractère principalement hydrophile.

9. Composition selon l'une quelconque des revendications précédentes, dans laquelle au moins l'une des membranes a un caractère principalement hydrophobe.

10. Composition selon l'une quelconque des revendications précédentes, dans laquelle de la nicotine et/ou un dérivé,

analogue, sel, solvate de nicotine ou un de leurs mélanges est libéré par le tabac ou le substitut du tabac.

11. Composition selon la revendication 10, dans laquelle la libération est une libération contrôlée.

12. Composition selon la revendication 10 ou 11, dans laquelle la nicotine et/ou un dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges est choisi dans l'ensemble constitué par la nor-nicotine, la lobéline, la méthylanabasine, l'anabasine, le chlorhydrate de nicotine, le dichlorhydrate de nicotine, le sulfate de nicotine, le monotartrate de nicotine, le bitartrate de nicotine, le salicylate de nicotine ou le zinc-chlorure de nicotine monohydraté.

13. Composition selon l'une quelconque des revendications précédentes, qui i) est conçue pour libérer de la nicotine et/ou un dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges en une quantité suffisante et/ou à un débit suffisant pour permettre un effet souhaité et ii) est conçue pour retenir les substances qui conduisent normalement à des effets secondaires et/ou pour libérer ces substances en une quantité sensiblement faible et/ou à un débit sensiblement faible.

14. Composition selon l'une quelconque des revendications précédentes, dans laquelle au moins l'une des membranes comprenant le matériau de membrane a une séparation des masses moléculaires d'environ 500 à environ 40 000, comme par exemple d'environ 500 à environ 5 000, d'environ 800 à environ 4 000, d'environ 1000 à environ 3 500, ou d'environ 2 000 à environ 40 000, d'environ 3 000 à environ 30 000, d'environ 5 000 à environ 25 000, d'environ 7 500 à environ 20 000 ou d'environ 10 000 à environ 20 000.

15. Composition selon l'une quelconque des revendications précédentes, dans laquelle au moins l'une des membranes comprenant le matériau de membrane a une épaisseur d'environ 2 à environ 200 μm, comme par exemple d'environ 5 à environ 100 μm, d'environ 7,5 à environ 50 μm, d'environ 7,5 à environ 40 μm, d'environ 7,5 à environ 35 μm, d'environ 7,5 à environ 30 μm ou d'environ 7,5 à environ 25 μm.

16. Composition selon l'une quelconque des revendications précédentes, dans laquelle au moins 50 % en poids de la teneur totale en nicotine et/ou dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges est libéré au plus dans les 60 minutes quand elle est soumise au test de libération décrit ici.

17. Composition selon l'une quelconque des revendications 1 à 15, dans laquelle au plus 25 % en poids de la teneur totale en nicotine et/ou dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges est libéré au plus dans les 60 minutes quand elle est soumise au test de libération décrit ici.

18. Composition selon l'une quelconque des revendications 1 à 15 ou 17, dans laquelle environ 50 % en poids de la teneur totale en nicotine et/ou dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges sont libérés au plus dans les 120 minutes quand elle est soumise au test de libération décrit ici.

19. Composition selon l'une quelconque des revendications précédentes, dans laquelle la libération de nicotine et/ou dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges à partir du tabac ou du substitut de tabac a les caractéristiques suivantes :
Temps (min) % en poids libéré de la teneur totale en nicotine
0 d'environ 0 à environ 20, comme par exemple d'environ 0 à environ 15 ou d'environ 0 à environ 10
3 d'environ 0,5 à environ 40, comme par exemple d'environ 0,5 à environ 35, d'environ 0,5 à environ 30, d'environ 1 à environ 25 ou d'environ 1 à environ 20
30 d'environ 2 à environ 65, comme par exemple d'environ 2 à environ 60, d'environ 5 à environ 60, d'environ 5 à environ 55, d'environ 7,5 à environ 55 ou d'environ 10 à environ 50
90 d'environ 10 à environ 100, comme par exemple d'environ 10 à environ 95, d'environ 15 à environ 90, d'environ 20 à environ 90, d'environ 25 à environ 85, d'environ 30 à environ 80, d'environ 35 à environ 80 ou d'environ 40 à environ 80
180 d'environ 40 à environ 100, comme par exemple d'environ 45 à environ 100, d'environ 50 à environ 100, d'environ 55 à environ 100, d'environ 60 à environ 100, d'environ 65 à environ 100 ou d'environ 70 à environ 100
et la libération est déterminée comme décrit ici.

20. Composition selon l'une quelconque des revendications précédentes, dans laquelle la libération de nicotine et/ou dérivé, analogue, sel, solvate de nicotine
ou un de leurs mélanges à partir du tabac ou du substitut de tabac a les caractéristiques suivantes :

Temps (min)	% en poids libéré de la teneur totale en nicotine
0	d'environ 0 à environ 15
3	d'environ 1 à environ 25
30	d'environ 7,5 à environ 55
90	d'environ 35 à environ 80
180	d'environ 65 à environ 100

et la libération est déterminée comme décrit ici.

21. Composition selon l'une quelconque des revendications précédentes, dans laquelle la libération de nicotine et/ou dérivé, analogue, sel, solvate de nicotine
ou un de leurs mélanges à partir du tabac ou du substitut de tabac a les caractéristiques suivantes :

Temps (min)	% en poids libéré de la teneur totale en nicotine
0	d'environ 0 à environ 10
3	d'environ 1 à environ 20
30	d'environ 10 à environ 50
90	d'environ 40 à environ 90
180	d'environ 70 à environ 100

et la libération est déterminée comme décrit ici.

22. Composition selon l'une quelconque des revendications précédentes, dans laquelle la libération de nicotine et/ou dérivé, analogue, sel, solvate de nicotine
ou un de leurs mélanges à partir du tabac ou du substitut de tabac a les caractéristiques suivantes :

Temps (min)	% en poids libéré de la teneur totale en nicotine
0	d'environ 0 à environ 10
3	d'environ 1 à environ 20
30	d'environ 30 à environ 50
90	d'environ 65 à environ 90

et la libération est déterminée comme décrit ici.

23. Composition selon l'une quelconque des revendications précédentes, dans laquelle le tabac est transformé à partir des feuilles de la famille de plantes *Solanaceae* et du genre *Nicotiana,* comme par exemple *Nicotiana tabacum* et *Nicotiana rustica.*

24. Composition selon l'une quelconque des revendications précédentes, comprenant de la nicotine et/ou un dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges selon la revendication 12, conjointement avec du tabac sous la forme de tabac à priser et/ou une substance de charge appropriée.

25. Composition selon l'une quelconque des revendications précédentes, laquelle composition comprend en outre des édulcorants, des arômes, des additifs de goût, des détergents, des substances d'ajustement du pH, des conservateurs, des tampons, des agents modifiant la libération et/ou des charges.

26. Composition selon l'une quelconque des revendications précédentes, laquelle composition comprend en outre des composés chimiques qui permettent et amplifient la libération de nicotine à partir du tabac, comme par exemple des tampons de régulation du pH, par exemple de l'huile de tampons carbonates, des solvants organiques et des extraits d'herbes.

27. Composition selon l'une quelconque des revendications précédentes, dans laquelle le tabac ou le substitut du tabac contient de la nicotine et/ou un dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges à une concentration d'environ 0 % en poids à environ 30 % en poids, comme par exemple d'environ 0,5 % en poids à environ 25 % en

poids, d'environ 0,1 % en poids à environ 20 % en poids, d'environ 0,1 % en poids à environ 15 % en poids, d'environ 0,1 % en poids à environ 10 % en poids, d'environ 0,1 % en poids à environ 9 % en poids ou d'environ 0,1 % en poids à environ 8 % en poids.

28. Composition selon l'une quelconque des revendications précédentes, dans laquelle le matériau de membrane est composé d'au moins deux types de membranes en ce qui concerne par exemple l'épaisseur, la séparation des masses moléculaires, la nature hydrophile/hydrophobe et la perméabilité à l'eau.

29. Composition selon l'une quelconque des revendications précédentes, laquelle composition a une taille et/ou une forme qui conviennent pour une application sous la lèvre supérieure d'un humain.

30. Composition selon l'une quelconque des revendications précédentes, contenant un mélange de tabac et d'un substitut du tabac.

31. Composition selon l'une quelconque des revendications précédentes, destinée à être utilisée en tant que substitut du tabac à fumer.

32. Composition selon la revendication 30 ou 31, destinée à être utilisée pour réduire l'état de manque à la nicotine et/ou l'abstinence à la nicotine.

33. Procédé pour contrôler la libération de nicotine et/ou d'un dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges, à partir de tabac ou d'un substitut du tabac dans la cavité orale, le procédé comprenant l'encapsulation d'un matériau choisi dans l'ensemble constitué par le tabac et le tabac en combinaison avec un substitut du tabac dans un matériau de membrane comprenant une ou plusieurs membranes, au moins l'une de celles-ci étant perméable à l'eau et insoluble dans l'eau, de façon que la nicotine et/ou le dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges soit libéré en une quantité suffisante et/ou à un débit suffisant pour i) permettre un effet souhaité et ii) retenir les substances qui conduisent normalement à des effets secondaires et/ou libérer ces substances en une quantité sensiblement faible et/ou à un débit sensiblement faible.

34. Procédé pour délivrer de la nicotine et/ou un dérivé, analogue, sel, solvate de nicotine ou un de leurs mélanges à une personne en ayant besoin, le procédé comprenant l'application d'une composition selon l'une quelconque des revendications 1 à 32 dans la cavité orale.

35. Procédé pour arrêter de fumer, le procédé comprenant l'application d'une composition selon l'une quelconque des revendications 1 à 32 à la cavité orale.

36. Utilisation d'une composition selon l'une quelconque des revendications 1 à 32 dans la fabrication d'un médicament pour réduire l'état de manque à la nicotine, par application de ladite composition à la cavité orale.

37. Utilisation d'une composition selon l'une quelconque des revendications 1 à 32 dans la fabrication d'un médicament pour réduire les effets secondaires liés au fait de fumer et/ou de priser du tabac, par application de ladite composition à la cavité orale.

38. Utilisation d'une composition selon l'une quelconque des revendications 1 à 32, en alternative et/ou en remplacement du tabac à fumer.

39. Procédé pour la préparation d'une composition selon l'une quelconque des revendications 1 à 32, le procédé comprenant l'encapsulation de tabac et/ou d'un substitut du tabac dans un matériau de membrane comprenant une ou plusieurs membranes, dont au moins l'une est une membrane perméable à l'eau et insoluble dans l'eau.

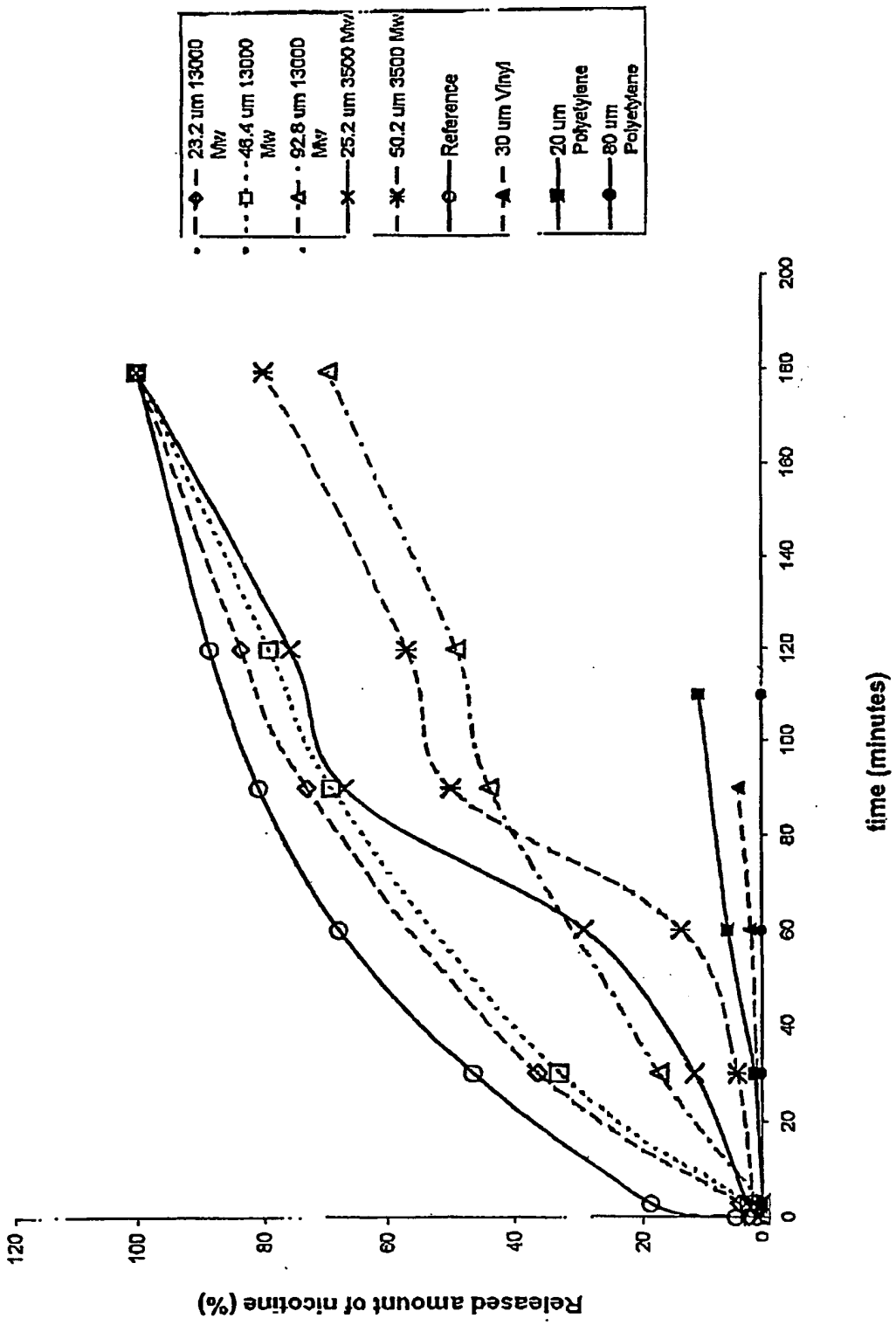
23.2 um 13000 Mw
48.4 um 13000 Mw
92.8 um 13000 Mw
25.2 um 3500 Mw
50.2 um 3500 Mw
Reference
30 um Vinyl
20 um Polyetylene
80 um Polyetylene
Released amount of nicotine (%)
time (minutes)
0
20
40
60
80
100
120
140
160
180
200

Fig. 1

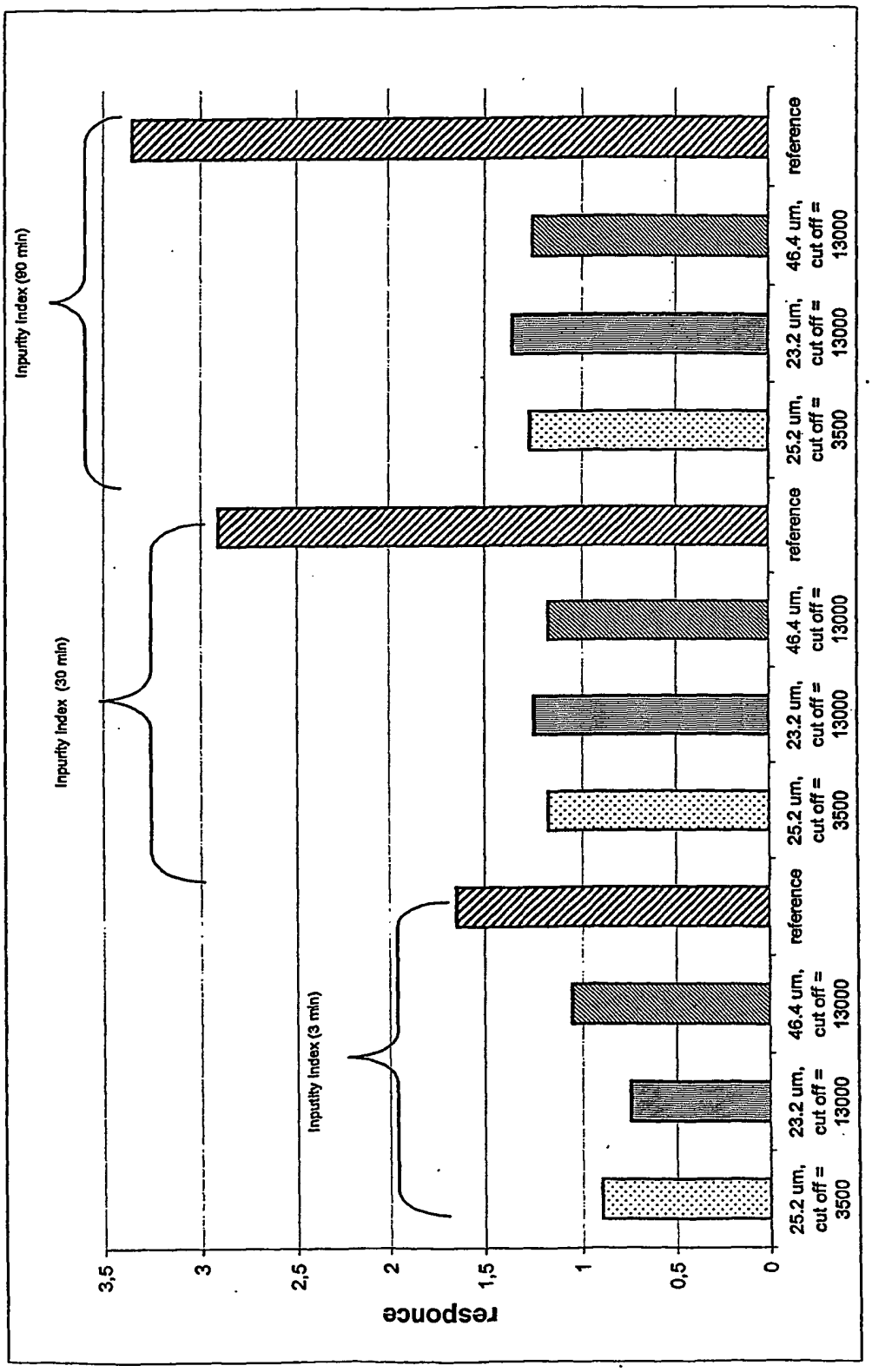
Inpurity index (90 min)
Inpurity index (30 min)
Inpurity index (3 min)
responce
3,5
3
2,5
2
1,5
1
0,5
0
reference
46.4 um, cut off = 13000
23.2 um, cut off = 13000
25.2 um, cut off = 3500

Fig. 2

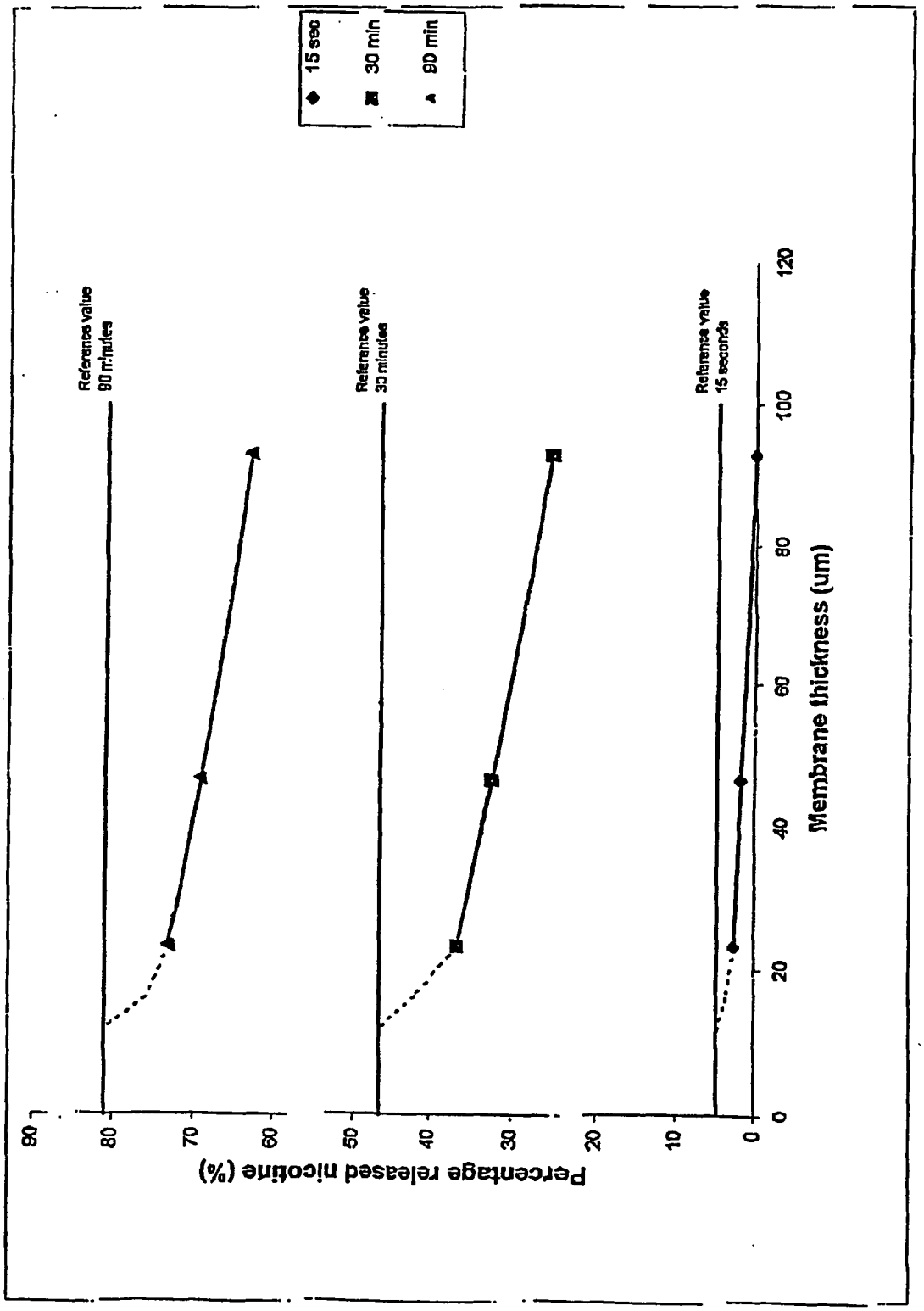
15 sec
30 min
90 min
Reference value 90 minutes
Reference value 30 minutes
Reference value 15 seconds
Percentage released nicotine (%)
Membrane thickness (um)
90
80
70
60
50
40
30
20
10
0
120
100
80
60
40
20
0

Fig. 3

REFERENCES CITED IN THE DESCRIPTION

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