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(19)

(54) SMOKING SUBSTITUTES AND METHOD OF PRODUCING SAME

(71) We, AKTIEBOLAGET LEO, a Swedish Corporation of 166, Langvinkelsgatan, Halsingborg, Sweden do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to smoking substitutes that are chewed and that are of particular value for facilitating a person's withdrawal from smoking and/or for decreasing a person's desire to smoke.

The administration of nicotine can give satisfaction and the usual method is by smoking, either cigarette smoking, cigar smoking, or pipe smoking. However, smoking may have health hazards and so it would be desirable to formulate an alternative manner of administering nicotine in a pleasurable manner that can be used to facilitate withdrawal from smoking and/or as a replacement for smoking.

Compositions containing nicotine or alkaloids having a similar effect and which can be chewed or sniffed are known but generally are not very satisfactory. Examples of such compositions are found in U.S. Patents Nos. 865,026 and 904,521.

These patents are mostly concerned with mixing finely ground tobacco, for instance snuff, into chewing gum, but the use of a tobacco extract of unidentified composition is also mentioned. However, we have found that when nicotine or other tobacco alkaloid is incorporated into an ordinary gum composition of the type that is most used and accepted today, the release of the alkaloid takes place very quickly. This is disadvantageous for two reasons: firstly, if the alkaloid is released too quickly, higher blood concentrations of the alkaloid are produced than with ordinary smoking, and secondly, the substitute has too short an effect.

It has been our object to device a chewable composition in which a tobacco alkaloid such as nicotine or a related alkaloid is released slowly, the composition thereby imitating satisfactorily the effect of the administration of nicotine by smoking.

The term " tobacco alkaloid " as used herein and in the claims is taken to mean nicotine or nicotine-like alkaloid such as nor-nicotine, or lobeline, in the free base or pharmacologically acceptable acid addition salt form. Source for alkaloids of this type are species of *Nicotiana* for nicotine and nor-nicotine the species *Lobeliaceae* (Indian tobacco) for lobeline; as is well known in the art.

An ideal smoking substitute in the form of a chewing gum should have the following properties:

(a) The release of the tobacco alkaloid should take place rather uniformly during not too short a period of time.

(b) The release of the tobacco alkaloid should take place rather uniformly when using different gum compositions.

(c) It should be possible without changing the gum composition to change the release rate of the tobacco alkaloid, for instance when employing smaller quantities of the alkaloid it may be desirable to increase somewhat the release rate in order to give a better satisfaction to the person who is using the substitute in question.

(d) The released alkaloid should produce a " feeling of smoking " not only after absorption into the blood stream but also in the mouth. This is very important because if the alkaloid is absorbed without producing much of a sensation in the mouth, this may lead to an excessive use of the substitute with less smoking satisfaction, and, thus, lead to return to ordinary smoking.

(e) The procedure of incorporating the alkaloid into the chewing gum should be easy to perform and also assure the substantially uniform distribution of alkaloid into the chewing gum.

It has now surprisingly been found that all these advantages are obtained if a tobacco alkaloid is bound to a cation exchanger and in this form is incorporated into chewable gum compositions in an amount effective to provide smoking satisfaction. The present invention

[*Price 25p*]

contemplates a smoking substitute composition comprising a gum base and a tobacco alkaloid held by a cation exchanger dispersed therein. The amount of tobacco alkaloid such as nicotine, nor-nicotine, lobeline, or mixtures thereof, present per chewable gum unit can vary over a wide range and can be present in an amount in the range of about 0.05 weight percent to about 2 weight percent, based on the weight of gum base and calculated as the free base. Usually a chewable gum unit contains about 1 to 10 milligrams of an alkaloid, preferably about 1 to about 5 milligrams. Preferably the smoking substitute composition is rendered acidic by the adidtion of a pharmacologically acceptable acidifying agent.

When the alkaloid bound to cation exchangers is incorporated into the chewing gum mass it is possible to use a wide variety of chewing gum compositions. A manufacture of chewing gums can thus incorporate the solid complex of alkaloid bound to a cation exchanger into his own composition without having to change the same and it is also possible to satisfy different taste preferences.

Release rate of the alkaloid from the composition can be varied by varying the amount of alkaloid that is bound to a given quantity of cation exchanger. A relatively higher amount of the alkaloid present in the composition gives a quicker release and vice versa. By the term "slow release" as used herein is meant that the major portion of the alkaloid is released from the smoking substitute composition substantially uniformly over a period of several minutes and preferably over a period of at least 10 minutes. Most preferably the release time is at least 20 minutes.

It is generally known that nicotine is absorbed from mucous membranes in the form of nicotine base. It has now been found that the "feeling of smoking" is weaker, if the alkaloid is released from the gum as the base. This is presumably due to the fact that the alkaloid is absorbed very readily at the chewing site, that is the part of the mouth that is in direct contact with the chewing gum. Thus only a relatively small amount of the alkaloid is transported to other parts of the mouth including the throat. The throat seems to be very sensitive to nicotine. If, as is the case with the present composition, nicotine is liberated as the nicotine cation, the absorption does not take place so quickly, thus allowing some of the nicotine to reach other parts of the buccal cavity including the throat, whereby some of the sensations of smoking are obtained, including a light burning sensation, which the smoker generally estimates in a positive way.

The complex containing an alkaloid bound to the cation exchanger is preferably prepared in a special unit. The solid complex thus prepared is easy to handle and minimizes personnel risks involved in the manufacture of the final chewing gum product. It has also been shown that the complex acts as a lubricant thereby facilitating the mixture of the different solid ingredients before incorporation into the gum mass. A homogenous product is easily obtained in this manner.

The ion exchanger must have cation exchanging groups in order to form the alkaloid-ion exchanger complex. Preferably, before formation of the complex, these groups are in the hydrogen ionic form.

The exchanger can also contain anionic groups, in which event it is known as a polyampholyte.

The cation exchanging groups that are present may be strongly acidic, weakly acidic or of intermediate acidity, synthetic cation exchangers containing these groups accordingly being called strongly acidic, weakly acidic or intermediate acidic cation exchangers, depending on the strength of the acid from which these functional groups are derived. Examples of suitable acidic groups that may be present are carboxylic, sulphonic acid, phosphonous acid, phosphonic acid, phosphoric acid, iminodiacetic acid, or phenolic groups. When the groups are phenolic groups then preferably their arrangement or content is such that the acidic strength is comparatively high. Ion exchangers containing such phenolic groups are disclosed by Adams, B.A. and Holmes, E.L., J. Soc. Chem. Ind. *54*, IT (1935). It is possible to obtain any desired pattern of release simply by using a suitable mixture of counterions in the same ion-exchanger or a suitable mixture of different ion-exchangers, the real compound ion-exchangers, polyampholytes, included. It is also possible to vary the pattern of release by altering the amount of alkaloid which is bound to a given amount of ion exchanger.

It is of course necessary that the cation exchanger, which is generally synthetic, should be non-toxic in the amounts used and it should not be such as to give an undesirable taste to the compositions. However these requirements do not present any serious problem since the amount of ion exchanger required for binding a sufficient amount of nicotine or other alkaloid in suitable compositions according to the invention is small.

The acidic groups of the ion exchanger, which may be termed an ion exchange resin, may be bound to a cross-linked polymer such as addition polymers of styrene and divinylbenzene, divinylbenzene and methacrylic acid, divinylbenzene and acrylic acid, phenolic resins, or cellulose, dextran or pectin cross-linked with, e.g., epichlorhydrine.

The acidic groups can be bound to insoluble linear polymers, e.g., cellulose with nitrous gases, whereby mainly uronic acid groups are formed. Such compounds are disclosed by Ott, E. and Spurlin, H.M., Cellulose and Cellulose Derivatives, Part I, Inter-science, New York (1954). Carboxymethyl cellulose, sulphoethyl

cellulose or cellulose sulphate, can also be used. In order to ensure that cellulose polymers containing the acidic groups are insoluble in the saliva, it is necessary that the number of acidic groups be relatively low, e.g., a maximum of 1 per 3 glucose units. Such compounds are disclosed by Ott, E. and Spurlin, H.M., Cellulose and Cellulose Derivatives, Part II, Interscience, New York (1954). Representative cation exchangers suitable for use according to the invention are given in Table I.

TABLE I

Representative Cation Exchangers in Accord with the Foregoing

Name	Type Cross Linked Polymer	Functional Groups	Manufacturer
Amberlite IRC 50	Divinylbenzene-methacrylic acid	Carboxylic	Rohm & Hass Co.
Amberlite IRP 64	— „ —	— „ —	— „ —
Amberlite IRP 64M	— „ —	— „ —	— „ —
BIO-REX 70	Divinylbenzene-acrylic acid	— „ —	BIO-RAD Lab.
Amberlite IR 118	Styrene-divinylbenzene	Sulfonic	Rohm & Haas Co.
Amberlite IRP 69	— „ —	— „ —	— „ —
Amberlite IRP 69M	— „ —	— „ —	— „ —
BIO-REX 40	Phenolic	— „ —	BIO-RAD Lab.
Amberlite IR 120	Styrene-divinylbenzene	— „ —	Rohm & Haas Co.
Dowex 50	— „ —	— „ —	Dow Chemical Co.
Dowex 50W	— „ —	— „ —	— „ —
Duolite C 25	— „ —	— „ —	Chemical Process Co.
Lewatit S 100	— „ —	— „ —	Farbenfabriken Bayer
Ionac C 240	— „ —	— „ —	Ionac Chemical Co.

TABLE 1 (continued)

Name	Type Cross Linked Polymer	Functional Groups	Manufacturer
Wofatit KPS 200	— „ —	— „ —	I. G. Farben Wolfen
Amberlyst 15	— „ —	— „ —	Rohm & Haas Co.
Duolite C-3	Phenolic	— „ —	Chemical Process Co.
Duolite C-10	— „ —	— „ —	— „ —
Lewatit KS	Phenolic	Sulfonic	Farbenfabriken Bayer
Zerolit 215	— „ —	— „ —	The Permutit Co.
Duolite ES-62	Styrene-divinylbenzene	Phosphonous	Chemical Process Co.
BIO-REX 63	— „ —	Phosphonic	BIO-RAD Lab
Duolite ES-63	— „ —	— „ —	Chemical Process Co.
Duolite ES-65	Phenolic	Phosphoric	— „ —
Chelex 100	Styrene-divinylbenzene	Iminodiacetic	BIO-RAD Lab
Dow Chelating Resin A-1	— „ —	— „ —	Dow Chemical Co.
CM Sephadex C-25	Dextran	Carboxy methyl	Pharmacia Fine Chemicals
SE Sephadex C-25	— „ —	Sulphoethyl	— „ —

Amberlite, Bio-Rex, Dowex, Duolite, Lewatit, Amberlyst, Dow and Sephadex, used above and below, are all Registered Trade Marks.

We set out below the properties and characteristics of four ion exchange resins that we have found to be of particular suitability in the invention and which are discussed frequently elsewhere in the specification.

No.	Name	Manufacturer
1.	Amberlite IRP 64	Rohm & Haas Co., Philadelphia
2.	Amberlite IRP 64M	— „ —
3.	Amberlite IRP 69M	— „ —
4.	BIO-REX 63	BIO-RAD Lab., Richmond, California

No.	Type	Functional groups
1.	Weakly acidic, methacrylic Type	Carboxylic $R.COO^-H^+$
2.	— „ —	— „ —
3.	Strongly acidic, polystyrene Type	Sulfonic $R.SO_3^-H^+$
4.	Intermediate acidic, polystyrene Type	Phosphonic $R.PO_3^-(H^+)_2$

No.	Ionic Form	Cross-linkage, % divinylbenzene
1.	Hydrogen	Not published, but according to the manufacturer this resin "While a gel resin" reacts as a "relatively high porosity" resin.
2.	— „ —	— „ —
3.	Sodium converted to hydrogen	Not published, but according to the manufacturer this resin reacts as a "conventional gel porosity" resin.
4.	— „ —	Not published, but according to the manufacturer this resin reacts as a "large porosity" resin.

No.	Apparent pK Value in One Molar Potassium Chloride Solution	Exchange Capacity meq/gm of Oven Dried Resin
1.	About 6.0	10.3
2.	— „ —	— „ —
3.	About 1.3	5.2
4.	Not published	6.6

No.	Particle size μ	Percent External Water
1.	150—40	Maximum 5.0
2.	95%<40	— „ —
3.	95%<40	Maximum 10.0
4.	150—75	Maximum 4.0

The amount of the alkaloid, e.g., nicotine, nor-nicotine, lobeline, acid addition salts thereof, or mixtures thereof bound to the ion exchanger may be varied depending on the conditions employed and the type of ion exchanger used.

Thus it has been found that alkaloid-ion exchange complexes in which the content of nicotine or other alkaloid amounts to about 2 to 60 percent, and preferably about 5 to 35 percent of the alkaloid to the ion exchange complex, are suitable for incorporation into the compositions of the invention. For carboxylic acid group containing ion exchangers, the preferred range is about 5 to 35 percent, whereas for phosphonic acid group containing ion exchangers the preferred range is about 5 to 30 percent, and the preferred range for sulphonic acid group containing ion exchangers is about 5 to 25 percent.

Part of the nicotine, nor-nicotine, lobeline or mixtures thereof may occur bound to the ion exchanger through surface adsorption as opposed to real ion exchange reaction.

Suitable and preferred amounts of various alkaloids for the formation of the ion exchange resin complexes for use in the invention are set out below.

Alkaloid-ion exchange complex	Percent alkaloid by weight in complex
Amberlite IRP 64M nicotine complex	2 — 60 preferably 5 — 35
Amberlite IRP 64M nor-nicotine complex	2 — 60 preferably 5 — 35
Amberlite IRP 64M lobeline complex	2 — 60 preferably 5 — 35
Amberlite IR 118 nicotine complex	2 — 35 preferably 5 — 20
BIO-REX 63 nicotine complex	2 — 40 preferably 5 — 30
BIO-REX 63 nor-nicotine complex	2 — 40; preferably 5 — 30
BIO-REX 63 lobeline complex	2 — 40; preferably 5 — 30

Alkaloid-ion exchange complex	Percent alkaloid by weight in complex
Amberlite IRP 69M nicotine complex	2 — 35; preferably 5 — 25
Amberlite IRP 69M nor-nicotine complex	2 — 35; preferably 5 — 25
Amberlite IRP 69M lobeline complex	2 — 35; preferably 5 — 25
Amberlite IRP 64 nicotine complex	2 — 60; preferably 5 — 35
Amberlite IRC 50 nicotine complex	2 — 60; preferably 5 — 35
Amberlite IRP 69 nicotine complex	2 — 35; preferably 5 — 25
BIO-REX 40 nicotine complex	2 — 25; preferably 5 — 15
BIO-REX 70 nicotine complex	2 — 60; preferably 5 — 35
Duolite ES-62 nicotine complex	2 — 35; preferably 5 —25
Duolite ES-65 nicotine complex	2 — 25; preferably 5 — 15
Chelex 100 nicotine complex	2 — 25; preferably 5 — 15
CM Sephadex C-25 nicotine complex	2 — 30; preferably 5 — 20
SE Sephadex C-25 nicotine complex	2 — 15; preferably 5 — 10

The chewing gum component of the compositions of the invention may be of any convenient nature and preferably is of a generally available commercial type. For example it can comprise a gum base of natural or synthetic origin. Natural gum bases include, e.g., Chicle-, Jelutong-, Lechi di Caspi-, Soh-, Siak-, Katiau-, Sorwa-, Balata-, Pendare-, Perillo-, Malaya- and Percha gums, natural caoutchouc such as Crepe, Latex and Sheets, and natural resins such as Dammar and Mastix. Synthetic gum bases are polyvinylacetate (" Vinnapas "), " Dreyco " commercial gum base, polyvinyl esters, polyisobutylene and non-toxic butadienestyrene lattices among others. Softeners (plasticizers) are, as is conventional in the art, incorporated into the commercially available chewing gum base to help reduce the viscosity of the rubber blend to a desirable consistency and to improve the texture. Some of the common softeners or plasticizers are: lecithin, lianolin, hydrogenated coconut oil, hydrogenated cotton seed oil, mineral oil, olive oil, vaseline, Carnauba wax, Candelilla wax, paraffin, beeswax, stearic acid, glyceryl monostearate, glycerine, honey, propylene glycol, hexylene glycol and sorbitol. These softeners also act as moisture-retaining agents at the same time. Miscellaneous other optional additives in a chewing gum composition are: cerelose, mannitol, diastatic malt, starch, calcium carbonate, talcum, defatted cocoa, flavors and food colors. Sugar in the form of sucrose and commercial glucose (corn syrup) comprises the bulk of a chewing gum formula, but completely sugar — and/or glucose-free chewing gum compositions work equivalently in the present invention.

For the purposes of the present invention the chewing gum component can be formulated with the following constituents which are present in varying amounts. The gum base can be of natural or synthetic origin, preferably the latter, and can be present in the chewing gum formulation in an amount in the range from 15 to 80 weight percent, preferably from 50 to 80 percent and most preferably from 60 to 75 weight percent.

Powdered sugar, preferably powdered sorbitol, can be present in an amount in the range from 15 to 80 weight percent, preferably from 16 to 40 weight percent, and most preferably from about 20 to about 32 weight percent.

Corn syrup usually of about 41° to 46° Baumé, preferably an about 70 percent aqueous solution of sorbitol, can be present in an amount in the range from about 4 to about 30 weight percent, preferably from about 4 to about 10 weight percent, and most preferably from about 5 to about 8 weight percent.

Special formulas for chewing gums exist, such as sugar-free compositions with a concentration of as much as 80 per cent chewing gum base, preferably of synthetic origin (Preparation 13, below).

Variations of the consistency, on the one hand the preliminary consistency at the very beginning of the chewing, and on the other hand the secondary consistency after some chewing, is achieved simply by varying amounts and proportions of the above formula. The consistency and the stickiness of the chewing gum can be influenced by the addition of various substances, as previously mentioned.

Compositions according to the invention can be formed simply by mixing the chewing gum mass with the alkaloid-ion exchanger complex, preferably together with an excess of a suitable acidifying agent. If the complex is in the form of a small particle size ion exchanger in the first place, then this can be mixed with the gum. If, however, the complex is in the form of a coarser ion exchanger then it is desirable to grind and size this first. The mixing is preferably conducted at a suitable elevated temperature depending upon the viscosity of chewing gum mass employed, since the increased temperature decreases the viscosity of the gum and thereby enables the alkaloid-ion exchanger complex to be evenly and intimately distributed into the chewing gum. The complex particle size in the gum should be small enough not to cause damage to teeth during chewing, however.

Conveniently compositions of the present invention are made simultaneously with the incorporation of any additives such as corn syrup, sugar, sorbitol, and flavors into the chewing gum base. Thus, for example, the composition can be made in a suitable kettle, for example, a steam jacketed mixer, which is warmed and the gum base added and mixed until sufficiently free from lumps. Next, sorbitol or corn syrup and sugar are incorporated into the base.

Depending on the physical properties of the pharmacologically acceptable acid that may be incorporated as an additional ingredient according to this invention, it will be convenient to add this acid, as in the case of, for instance, sulphuric acid, with the liquid part of sorbitol or with the corn syrup. In the case of, for instance, malic acid, it will be convenient to add this particular acid with the solid, powdered part of sorbitol or sugar. Finally, flavors, softeners and other additives are poured in and well distributed. The mass is cooled, rolled, scored, and hardened sufficiently, then coated if desired, before final wrapping and analyzing. Controlled humidity rooms assure consistent moisture content and prevent " sweating " of the gum. It is preferred to use just enough heat to soften the gum base sufficiently for mixing. The addition of sugar and syrup tends to lower the temperature, and the various alkaloid-ion ex-

change complexes together with flavor, if desired, are added only when the mixture has cooled sufficiently. This minimizes uncontrollable losses in alkaloid and/or flavor content to a marked degree.

The weight of one chewing gum unit, e.g., stick, ball, or the like, according to the present invention, can be varied between 0.5 and 4.0 grams and preferably between 1.0 and 3.0 grams, as is generally conventional in the chewing gum art.

The percent by weight of the various alkaloid ion exchange complexes, either each or mixtures thereof, to the total weight of the gum, is not critical but varies between an upper and a lower most suitable range, specific to the formula used. Thus it has been found that compositions, wherein the percent by weight of the alkaloid ion exchange complex to the total weight of the gum is about 0.1 to 10 percent, preferably about 0.2 to 5 percent, and most preferably about 0.5 to 2 percent, are suitable.

Some Preparations and Examples are now given. Preparation 1 demonstrates the preparation of a suitable ion exchange complex while Preparations 2 to 13 demonstrate suitable chewing gum compositions. It should be realized from what has been said before that these compositions may not be preformed but may in fact be formed simultaneously with the incorporation of the complex into the compositions.

Preparation 1: A nicotine ion exchange complex containing 200 mg. of nicotine in 800 mg. of the ion-exchanger Amberlite IRP 64M in the dry state, i.e., a 20 percent compound (complex)

The moisture content of the ion exchanger is determined by drying in an oven at 105°C. to a constant weight.

100.0 grams of the ion exchanger, calculated as dry, are added to a beaker containing 25.0 grams nicotine, calculated as 100 percent, diluted to a total volume of 500 ml. by an addition of distilled water. The mixture is stirred for at least 1 hour with a magnetical stirrer, or the like. The loaded ion exchanger is then separated by filtration or centrifugation. The filtercake is then broken into pieces and dried at about 20°C. in a drying cabinet provided with a fan. The nicotine ion exchange complex thus obtained is then analyzed with reference to the nicotine content after careful blending and sieving through a 300 mesh sieve. (British Standad 410)

Preparation of the other various alkaloid ion exchange complexes mentioned below in accordance with the present invention is in accord with the foregoing example, or with only minor variations as are well known to one skilled in the art of handling ion-exchangers. All percentages indicated are by weight.

Preparation 2	
Granulated sugar	14.5 percent
Condensed sweetened milk (low in fat content)	4.5 percent
Powdered glucose	30.0
Chicle gum	20.0
Powdered sugar	30.0
Tolu-Balsam	1.0

Preparation 3	
Dreyco Commercial Gum Base (synthetic)	16.9 percent
Powdered glucose	22.5
Powdered sugar	60.0
Water	0.3
Glycerine	0.3

Preparation 4	
Natural gum base	22.0 percent
Powdered sugar	64.0
Corn syrup 45° Baumé	14.0
Preparation 5	
Natural gum base	22.0 percent
Diastatic malt	1.0
Corn syrup 44° Baumé	15.0
Powdered sugar	60.0
Calcium carbonate	2.0
Preparation 6	
Natural gum base	22.0 percent
Diastatic malt	2.0
Invert sugar	5.0
Corn syrup 44° Baumé	13.0
Powdered sugar	51.0
Cerelose	7.0
Preparation 7 (Summer Formula)	
Natural gum base	22.0 percent
Powdered sugar	50.0
Corn syrup 45° Baumé	24.0
Calcium carbonate	2.0
Powdered starch	2.0
Preparation 8 (Winter formula)	
Natural gum base	22.0 percent
Powdered sugar	53.0
Corn syrup 44° Baumé	21.0
Calcium carbonate	2.0
Powdered starch	2.0

Preparation 9 (Stick gum formula)	
Stick gum base	19.9 percent
Powdered sugar	54.5
Powdered glucose	9.9
Corn syrup 45° Baumé	14.9 percent
Glycerine	0.2 — 0.5
Flavoring oil	0.6

Preparation 10 (Bubble gum formula)	
Bubble gum base	18.0 percent
Powdered sugar	55.9
Powdered glucose	9.0
Corn syrup 45° Baumé	16.2
Glycerine	0.2 — 0.7
Flavoring oil	0.6

Preparation 11 (Sugar coated gum formula)	
Sugar coated gum base	22.0 percent
Powdered sugar	55.1
Powdered glucose	5.5
Corn syrup 45° Baumé	16.5
Glycerine	0.2 — 0.5
Flavouring oil	0.7

The gums are coated with white or colored sugar in rotating-pans in the usual manner for the coating of dragees.

Preparation 12 (Sugar-and glucose-free formula)	
Natural gum base	29.2 percent
Powdered sorbitol	45.8
Calcium carbonate	8.5
Sorbitol, 70 percent water solution	16.5

Preparation 13: Sugar- and glucose-free formula with high chewing gum base concentration.	
Synthetic gum base	73.7 percent
Powdered sorbitol	19.8
Sorbitol, 70 per cent water solution	3.8
Glycerin	0.7
Flavouring oil	2.0

The following Examples demonstrate the compositions according to the invention. Each of these is made by warming the gum base in a kettle and then adding the various additives, in the general method described above.

Example 1.

Chewing gum containing a 10 percent complex obtained from 3 mg. of nicotine bound to Amberlite IRP 64M. Chewing gum mass according to Preparation 4, 1000 pieces of gum per 1970 grams of the mass.

Amberlite IRP 64M 10 percent nicotine complex 30.0 grams.

Example 2.

Chewing gum containing a 10 percent complex, obtained from 2.5 mg. of nicotine bound to Amberlite IRP 64M, and likewise a 20 percent complex, obtained from 2.5 mg. of nicotine bound to Amberlite IRP 64M.

Chewing gum mass according to Preparation 4, 1000 pieces of gum per 1835 grams of the mass.

Amberlite IRP 64M 10 percent nicotine complex 25.0 grams.

Amberlite IRP 64M 20 percent nicotine complex 12.5 grams.

Example 3.

Chewing gum containing a 30 percent complex, obtained from 1 mg. of nicotine bound to Amberlite IRP 64M.

Chewing gum mass according to Preparation 6, 1000 pieces of gum per 3325 grams of the mass.

Amberlite IRP 64M 30 percent nicotine complex 3.33 grams.

Example 4.

Chewing gum containing a 20 percent complex, obtained from 3 mg. of nicotine bound to Amberlite IRP 69M.

Chewing gum mass according to Preparation 4, 1000 pieces of gum per 1485 grams of the mass.

Amberlite IRP 69M 20 percent nicotine complex 15.0 grams.

Example 5.

Chewing gum containing a 15 percent complex, obtained from 4 mg. of nicotine bound to BIO—REX 63, converted to the hydrogen ionic form.

Chewing gum mass according to Preparation 4, 1000 pieces of gum per 2025 grams of the mass.

BIO—REX 63 15 percent nicotine complex 26.7 grams

Example 6.

Chewing gum containing a 30 percent complex, obtained from 2 mg. of lobeline bound to Amberlite IRP 64M.

Chewing gum mass according to Preparation 3, 1000 pieces of gum per 3325 grams of the mass.

Amberlite IRP 64M 30 percent lobeline complex 6.67 grams.

Example 7.

Chewing gum containing a 20 percent complex, obtained from 1 mg. of lobeline bound to Amberlite IRP 64M, and likewise a 35 percent complex, obtained from 1 mg. of nicotine bound to Amberlite IRP 64M.

Chewing gum mass according to Preparation 12, 1000 pieces of gum per 1565 grams of the mass.

Amberlite IRP 64M 20 percent lobeline complex 5.0 grams.

Amberlite IRP 64M 35 percent nicotine complex 2.86 grams.

Example 8.

Chewing gum containing a 10 percent complex, obtained from 5 mg. of nor-nicotine bound to Amberlite IRP 64M.

Chewing gum mass according to Preparation 2, 1000 pieces of gum per 450 grams of the mass.

Amberlite IRP 64M 10 percent nor-nicotine complex 50.0 grams.

Example 9.

Chewing gum containing a 15 per cent complex, obtained from 2 mg. of nicotine bound to Amberlite IRP 69M.

Chewing gum mass according to Preparation 13, 1000 pieces of gum per 987 grams of the mass.

Amberlite IRP 69M 15 percent nicotine complex 13.33 grams.

Example 10.

Chewing gum containing a 15 per cent complex, obtained from 2 mg. of nicotine bound to Amberlite IRP 64M, and likewise a 10 percent complex, obtained from 1 mg. of nor-nicotine bound to Amberlite IRP 64M.

Chewing gum mass according to Preparation 4, 1000 pieces of gum per 2975 grams of the mass.

Amberlite IRP 64M 15 per cent nicotine complex 13.33 grams.

Amberlite IRP 64M 10 percent nor-nicotine complex 10.0 grams.

Preparation of chewing gums containing the other various alkaloid-ion exchange complexes mentioned in the present application, either separately or mixtures thereof, is carried out in the manner of the foregoing examples, with only such minor variations as are well known to every person skilled in the art of manufacturing chewing gums.

It is particularly surprising that slow and controlled release of the alkaloid is obtained in the compositions of the invention when one considers the results that we have obtained in prior experiments. Thus we have found previously that one does not obtain a satisfactory release rate for the alkaloid from alkaloid-ion exchange complexes in the absence of chewing gum. Table I below is a compilation of experimental results showing the amount of nicotine released as a function of time.

TABLE I

Released Nicotine in percent by Weight as a Function of Time

Composition / Time, min.	A1	A2	D	E
2	18%	18%	54%	64%
5	36%	39%	70%	66%
10	61%	65%	70%	66%
20	91%	92%	70%	66%

A1 - Chewing gum containing 20 milligrams Amberlite IRP 64M resin complexed with nicotine base (20 weight percent nicotine) and 1 gram chewing gum mass having a high gum base concentration, prepared in accordance with Preparation 13. Release brought about by chewing. Very pronounced feeling of smoking was observed.

A2 - Chewing gum containing 20 milligrams Amberlite IRP 64M complexed with nicotine base (20 weight percent nicotine) amd 3 grams chewing gum mass having a low gum base concentration, prepared in accordance with Preparation 4. Release brought about by chewing. Very pronounced feeling of smoking was observed.

D - Amberlite IRP 64M resin complexed with nicotine base (10 weight percent nicotine). Release brought about with 10 milliliters of synthetic saliva No. 2, *infra*, contacting 50 milligrams of the complex at 37°C.

E - Same complex as in D but release brought about with 10 millilitres of physiological saline solution contacting 50 milligrams of the complex at 37°C.

Detailed desorption and chewing tests have been conducted.

Desorption Tests

Desorption tests in vitro of alkaloid cation exchange complexes without incorporation into chewing gum mass have been made. In one series of experiments a quantity of 25 mg. of the cation exchange complex in question including 5 mg. of nicotine was shaken for different times with 10 ml. of water, physiological sodium chloride solution, 20 percent (w/v) sugar solution, and saliva. The shaking was carried out in a thermostat at 20±0.1°C and at 37±0.1°C. Samples of the filtered solution were analysed with reference to nicotine by UV-determination. The ion exchange resins Amberlite IRP 64M and IRP 69M were tested with the following results. However, the use of other ion exchangers in accordance with this invention produces similar results.

Results:
Total released quantity of nicotine in mg/10 ml.

Medium	Water				NaCl			
Ion Exchanger	IRP 64M		IRP 69M		IRP 64M		IRP 69M	
Temperature	20°	37°	20°	37°	20°	37°	20°	37°
Time, Minutes								
2	0.22				3.68		1.90	
5	0.23	0.21			3.88	4.01	1.93	2.00
10	0.23				3.96		1.95	
15	0.25				3.98		1.96	
20	0.25				3.98		1.97	
30	0.27	0.25	0.01	0.01	4.08	4.11	1.97	2.01

Medium	Sugar				Saliva 1			
Ion Exchanger	IRP 64M		IRP 69M		IRP 64M		IRP 69M	
Temperature	20°	37°	20°		20°	37°	20°	37°
Time, Minutes								
2	0.39							
5	0.46	0.43			2.94	3.40	2.24	2.21
10	0.47				3.21		2.26	
15	0.50							
20	0.50						2.30	
30	0.59	0.44	0.02		3.28	3.46	2.30	2.70

Medium	Saliva 2			
Ion Exchanger	IRP 64M		IRP 69M	
Temperature	20°	37°	20°	37°
Time, Minutes				
2	3.24			
5			1.51	
10	3.45	4.57		4.05
15				
20				
30	3.46	4.60	1.57	4.23

Media
Water: twice ion exchanged, distilled water
Physiological sodium chloride solution: 0.9 percent in distilled water

Sugar: Saccarose, 20 percent in water

Saliva 1:	Gelatine	2 g.
	Glycine	1 g.
	Aspartic acid	1 g.
	Phytin (Ciba)	0.5 g.
	$NaHCO_3$	1 g.
	NaCl	0.5 g.
	KSCN	0.1 g.
	Water	ad 1000 ml.
Saliva 2:	NaCl	0.45 g.
	$CaCl_2.6H_2O$	0.12 g.
	$CaCO_3$	1.0 g.
	Na_2HPO_4 (dried)	0.07 g.
	Mucin	2.5 g.
	Taka-diastase	16.0 g.
	Cholesterine	0.06 g.
	Water	ad 1000 ml.

From the results it will be apparent that the equilibrium is reached very quickly. After 2 minutes, no further release occurs. The addition of sugar does not influence the release. The ion exchange resin Amberlite IRP 69M appears to bind the nicotine stronger than the ion exchanger IRP 64M. The strength of the binding is of the same order in saliva and physiological sodium chloride solution, but considerably lower than in water and sugar solution.

No particular difference between the release at 20°C and 37° was found except in one case. The test with the artificial saliva 2 gave a more rapid release at the higher temperature. Said saliva solution 2 includes mucin, which is also present in human saliva. It therefore seems probable that the presence of mucin in human saliva gives a reasonable basis for explaining the unobvious effect of the initially rather rapid release of nicotine, nor-nicotine, lobeline, etc., which is noticed when smoking substitutes in accordance with the present invention are being chewed. Thus, without the presence of the mucin, the desorption could take place too slowly for any practical effect, especially from the standpoint of the creation of a proper and desirable taste " sensation ".

This pehnomenon seems to be particularly unobvious in the case of strongly acidic catio exchangers, e.g., Amberlite IRP 69M, in view of the fact that alkaloids are usually so strongly bound thereto that they can be eluted from such ion exchange complexes only with difficulty.

Chewing Tests

The results of the analysis with reference to nicotine shown below refer to chewing tests. Two persons chewed the gum at different times, the analytical results were tabulated, and the mean value determined.

The chewing gums in these tests refer to the following formula:

Natural gum base	22.0 percent
Powdered sugar	64.0
Corn syrup 45° Baumé	14.0

Each particular chewing gum is composed of 3.0 grams of this mass and a quantity of one of a variety of alkaloid-ion exchange complexes, as further disclosed below, each corresponding to 5.0 mg. of alkaloid.

The proportion between nicotine and the ion exchanger was varied with the different raw materials which are used in the samples below.

Example 11.

190 mg. of nicotine per g. of Amberlite IRP 64M nicotine complex.

Chewing time minutes	*Mean value nicotine released mg.*
0	0
2	1.9
5	2.6
10	3.2
15	3.3
20	4.2
30	4.4

Example 12.

105 mg. of nicotine per g. of Amberlite IRP 64M nicotine complex

Chewing time minutes	*Mean value nicotine released mg.*
0	0
2	0.6
5	1.2
10	2.3
15	2.7
20	3.3
30	4.1

Example 13.

179 mg. of nicotine per g. of Amberlite IRP 64 nicotine complex.

Chewing time minutes	*Mean value nicotine released mg.*
0	0
2	2.0
5	2.2
10	3.3
15	3.6
20	4.0
30	4.2

Example 14.

210 mg. of nicotine per g. of Amberlite IRP 69M nicotine complex.

Chewing time minutes	*Mean value nicotine released mg.*
0	0
2	2.3
5	2.6
10	3.5
15	4.1
20	4.3
30	4.7

Example 15.

333 mg. of nicotine per g. of Amberlite IRP 64M nicotine complex.

Chewing time minutes	*Mean value nicotine released mg.*
0	0
2	3.1
5	3.8
10	4.4
15	4.5
20	4.6
30	4.8

In the following Examples the chewing gum was prepared according to Preparation 13. Each piece of gum contains 1.0 gram of this composition.

Example 16.

170 mg. of nicotine per g. of Amberlite IRP 64M nicotine complex. 1.5 mg. nicotine per chewing gum.

Chewing time minutes	*Mean value nicotine released mg.*
0	0
2	0.02
5	0.26
10	0.70
15	0.98
20	1.14
30	1.32

Example 17.

175 mg. of nicotine per g. of Amberlite IRP 64M nicotine complex. 4 mg. nicotine per chewing gum.

Chewing time minutes	*Mean value nicotine released mg.*
2	0.72
5	1.44
10	2.44
20	3.64

Example 18.

88 mg. of nicotine per g. of BIO—REX 63 nicotine complex. 2 mg. nicotine per chewing gum.

Chewing time minutes	*Mean value nicotine released mg.*
0	0
2	0.13
5	0.17
10	0.50
20	1.25
30	1.68

To determine nicotine, nicotine has been quantitatively determined by titration with perchloric acid.

As identification test an IR-spectrum has been used.

Determination of Nicotine Bonded to Ion Exchangers

Method taken from Off. Meth. Anal. of the A.O.A.C. 9th ed. 1960 pp. 94—95.

Reagents. Alkali-salt solution. Dissolve 300 g NaOH in 700 ml water and saturate with NaCl.

Hydrochloric acid. Dilute conc. HCl 1 + 4 (one part conc. HCl diluted with 4 parts distilled water)

Apparatus. Steam distillation assembly (i.e., of the type used for nitrogen determination according to Kjeldahl). Spectrophotometer Beckman DU.

Determination. Weigh accurately sample corresponding to 5 mg. nicotine and transfer to the distillation flask. Place 50 ml hydrochloric acid (1 + 4) in a 500 ml volumetric flask, used as a receiver, placed so that the condenser tube dips into the solution. Add 50 ml alkali-salt solution to the sample in the distillation flask and steam distil as rapid as steam can be condensed efficiently. Effluent condensate should not be above room temperature. Apply heat to distillation flask to keep the volume in it constant. Collect some 480 ml condensate and dilute with water to volume.

Read absorbance in the spectrophotometer at 259 (max), 236 (min) and 282 mμ.

Calculate $E_{corr} = E_{max} - 1/2(E_{min} + E_{282})$

$E^{1\%}_{1\ cm}$ (corr) has been determined to be 338

$$\frac{E_{corr} \times 500 \times 1000}{338 \times 100 \times (\text{sample weight, g})}$$

=mg. nicotine/g sample.

Determination of Nicotine in Chewin Gum

Apparatus. Spectrophotometer Beckman DU.

Determination: Homogenize one chewing gum with a 20 g seasand in a mortar under ether. Transfer the homogenous mixture to a glass column with a glass wool plug at the bottom. Elute the column with ca. 100 ml ether and collect the eluate in a separation funnel. Make the column as free from ether as possible. Extract the ether in the separation funnel with 3 × 15 ml 0.1 N hydrochloric acid and combine the extracts in a 250 ml volumetric flask. The ether phase is then discarded. Elute the now nearly dry column with 0.1 N hydrochloric acid into the flask containing the combined extracts until the total volume is 250 ml.

Read absorbance in the spectrophotometer at 259 (max), 236 (min) and 282 mμ.

Calculate $E_{corr} = E_{max} - 1/2(E_{min} + E_{282})$

$E^{1\%}_{1\ cm}$ (corr) has been determined to be 338

$$\frac{E_{corr} \times 1000 \times 250}{338 \times 100}$$

=mg. nicotine/g chewing gum

The method is applicable also to chewed gums for determination of remaining nicotine.

Many ion exchangers according to given examples are suitable for use in the preparation of the smoking substitutes, and we have also given many examples of smoking substitute compositions according to the invention. We now give a detailed example of the preparation of one of the smoking substitutes.

Example 19.

A nicotine ion exchange complex with Amberlite IRP 64M was prepared by the method described in Preparation 1, the resultant complex containing 10% nicotine.

434 Grams natural gum base is put into a hot jacketed mixer fitted with stirrers. The mixer is heated by steam at about 15 lbs. per sq. inch. The stirrers are run at intervals to turn the base over. A low steam pressure is selected to prevent overheating of the base. After the base is completely melted, the steam is turned off in the mixer and cold water is run through the jacket to reduce the temperature of the contents to about 85°C. 840 Grams of powdered sugar (300 mesh sieve) and 276 grams corn syrup 45° Baumé are then added to the melted base in the mixer and the mass is mixed for about fifteen minutes. The mixture will now have a temperature of between 60 and 75°C.

A further 420 grams of powdered sugar and 30 grams of the nicotine ion exchange complex, both 300 mesh sieve, are mixed together and are then added as a powder mixture to the molten mixture in the kettle. The melt is mixed for a further five minutes, so that the total mixing time is about fifteen minutes.

The temperature in the kettle will at the end of this time have dropped to between 40 to

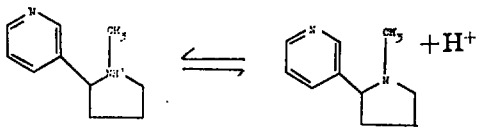
60°C. It is desirable that the mix should be as cool as possible before mixing stops, but viscosity increases as the temperature drops and mixing must stop before the mixture becomes too stiff for the mixing machine. In practice the operator judges when to stop mixing not so much by the actual thermometer reading as by the consistency of the mix.

After mixing, the batch of gum is cut into pieces of a size suitable for feeding to whatever type of extruder is available. The extruder jacket is usually heated by means of warm water at 45 to 50°C. This gives a more even extrusion than when the extruder is heated by steam and it permits better temperature control. The extruded stick of gum should be well dusted with starch or a mixture of icing sugar and starch to prevent it from sticking to sizing rollers and cutters. The rollers serve to roll it down to the desired size. The cutters are preferably maintained at about 25°C.

The precise manner of shaping the gum in the extruder and afterwards is however fairly conventional and will be selected according to the desired shape and size of the resultant pieces. Each piece generally weighs between 1 and 3 grams. In this Example, 1000 pieces, each weighing two grams, were provided by the conventional extruding and cutting procedure. Likewise, the pieces are packed and stored under fairly conventional conditions. For example the wrapping room is preferably maintained at 20°C and a relative humidity of 45 to 50% and the pieces are preferably stored at a temperature of 18 to 20°C and a relative humidity of 45 to 40%.

It will be appreciated that combinations of alkaloid ion exchange complexes with gum other than those demonstrated in the foregoing Examples can be used and that combinations with other flavouring agents, sweetening agents, binders and such additives can also be used.

As mentioned hereinabove, it is preferred that the smoking substitute compositions of this invention are acidic. This is desirable in order to enhance the feeling of smoking upon use of the present compositions, because in an acidic environment the nicotine cation-nicotine base equilibrium, i.e.,



is shifted to the left, further decreasing the nicotine absorption rate at the chewing site and allowing some of the released nicotine to reach other parts of the buccal cavity including the throat. It has been found that it is desirable, for the purposes of this invention, to maintain the pH at the chewing site at a pH of less than about 7, and preferably in the range from 5 to 4, by incorporating a pharmacologically acceptable acidifying agent into the composition.

In one preferred embodiment of this invention, the cation exchanger, initially in its ionic hydrogen form, is only partly loaded with nicotine or similar alkaloid when incorporated into a smoking substitute composition of this invention. Upon chewing such a composition, hydrogen ions are liberated from the cation exchanger and pH of saliva at the chewing site is decreased, which decrease in pH influences, in turn, the acid-base equilibrium. Similarly, it is possible to admix a fully nicotine-loaded cation exchange resin with a cation exchange resin in its acid form to bring about the desired acidity at the chewing site, or to admix a fully nicotine-loaded action exchange resin with a pharmacologically acceptable organic or inorganic acid, or to admix a fully nicotine-loaded cation exchange resin with a combination of a cation exchange resin in its acid form with a pharmacologically acceptable organic or inorganic salt.

The amount of pharmacologically acceptable acid present in the foregoing instances can be in the range of 1.5 to 10 equivalents of acid per mole of the alkaloid base, preferably about 1.5 to 6 equivalents of acid per mole of the alkaloid base, and most preferably 2 to 4 equivalents of acid per mole of the alkaloid base. Expressed in terms of the alkaloid present as neutral salt, the amount of acid present can be in the range of about 0.5 to about 9 equivalents of acid per mole of the neutral alkaloid salt, preferably about 0.5 to about 5 equivalents of acid per mole of the neutral alkaloid salt, and most preferably about 1 to about 3 equivalents of acid per mole of the neutral alkaloid salt.

For the purposes of the present invention suitable acids are inorganic acids such as hydrochloric acid, sulphonic acid or phosphoric acid, as well as organic acids such as succinic acid, fumaric acid, glutaric acid, adipic acid, malic acid, tartaric acid, ascorbic acid, citric acid or mixtures of the aforesaid acids. The organic acids are preferred.

The acid or acids may be incorporated directly into the gum composition at any convenient compounding stage thereof, or admixed beforehand with a water-soluble part of the composition, e.g., sorbitol, and then incorporated into the gum composition.

Tests, where substitutes according to the present invention have been given to habit smokers, have produced very good results. In several cases it has been possible for a known subject, by using 6 to 20 pieces of gum per day, to give up smoking completely and in other cases for the subject to reduce smoking considerably.

WHAT WE CLAIM IS:—

1. A chewing gum smoking substitute comprising dispersed in a chewing gum base a cation exchanger on which a tobacco alkaloid is held.

2. A substitute according to claim 1 in which the gum base is present in an amount of 15 to 80% by weight.

3. A substitute according to claim 2 in which the gum base is present in an amount of at least 50% by weight.

4. A substitute according to claim 3 in which the gum base is present in an amount of 60 to 75% by weight.

5. A substitute according to any preceding claim in which the alkaloid is nicotine or a pharmacologically acceptable salt thereof.

6. A substitute according to any of claims 1 to 4 in which the alkaloid is nor-nicotine or a pharmacologically acceptable salt thereof.

7. A substitute according to any of claims 1 to 4 in which the alkaloid is lobeline or a pharmacologically acceptable salt thereof.

8. A substitute according to any preceding claim in which the cation exchanger on which the alkaloid is held is of the methacrylic type, is weakly acidic and contains carboxyl functional groups.

9. A substitute according to any of claims 1 to 7 in which the cation exchanger on which the alkaloid is held is of the polystyrene type, is strongly acidic and contains sulphonic functional groups.

10. A substitute according to any of claims 1 to 7 in which the cation exchanger on which the alkaloid is held is of the polystyrene type of intermediate acidity and contains phosphonic functional groups.

11. A substitute according to any preceding claim in which the alkaloid is present in an amount of 0.05 to 2% by weight calculated as free alkaloid base.

12. A substitute according to any preceding claim which yields a pH of less than 7 on chewing.

13. A substitute according to claim 12 which yields a pH in the range of 4 to 5 on chewing.

14. A substitute according to claim 12 or claim 13 which includes as acidifying agent a pharmacologically acceptable acid present in an amount of 1.5 to 10 equivalents per mole of the alkaloid calculated as free alkaloid base.

15. A substitute according to claims 12 or 13 in which part of the cation exchanger is in the ionic hydrogen form and is present in an amount of 1.5 to 10 equivalents per mole of the alkaloid calculated as free alkaloid base.

16. A substitute according to claim 14 or claim 15 in which the acid or cation exchanger in ionic hydrogen form is present in an amount not greater than 6 equivalents per mole of the alkaloid calculated as free alkaloid base.

17. A substitute according to claim 16 in which the acid or cation exchanger in ionic hydrogen form is present in an amount of 2 to 4 equivalents per mole of the alkaloid calculated as free alkaloid base.

18. A substitute according to claim 1 substantially as described herein with reference to any of the Examples.

19. A method for making a substitute according to claim 1 comprising dispersing, in a gum base, a cation exchanger on which a tobacco alkaloid is held.

20. A method according to claim 19 substantially as described herein with reference to any of the Examples.

21. A substitute made by a method according to claim 19 or claim 20.

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