

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**18-612/S022**

**20-066/S004**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 18-612

December 13, 1994

Marion Merrell Dow  
P.O. Box 9627  
Kansas City, MO 64134-0627

Attention: Elaine Waller

Dear Ms. Waller

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Nicorette (nicotine polacrilex)

NDA Number: 18-612

Supplement Number: S-022

Date of Supplement: December 9, 1994

Date of Receipt: December 12, 1994

Should you have any questions, please contact

Sharon Schmidt  
Project Manager  
(301) 443-3741

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Sharon Schmidt".

For Project Manager  
Pilot Drug Evaluation Staff,  
HFD-007  
Center for Drug Evaluation and  
Research



MARION MERRELL DOW INC.

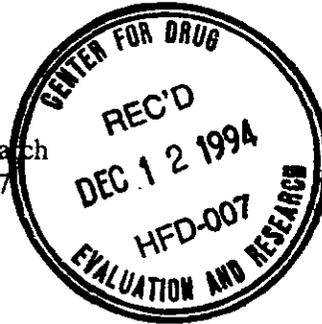
NDA NO. 18612 REF. NO. 022

NDA SUPPL FOR SEG

Marion Park Drive  
MAIL: P.O. Box 9627  
Kansas City, Missouri 64134-0627  
Telephone: 816-966-5000

December 9, 1994

Food and Drug Administration  
Center for Drug Evaluation and Research  
Pilot Drug Evaluation Staff, HFD-007  
Document Control Room: 9B-45  
5600 Fishers Lane  
Rockville, MD 20857



ORIGINAL



SUBJECT: NDA 20-066  
Nicorette® DS  
(nicotine polacrilex)

NDA 18-612 ✓  
Nicorette®  
(nicotine polacrilex)

Gentlemen:

This supplement to NDA 18-612 and NDA 20-066 contains information establishing the safe and effective use of Nicorette® in an over-the-counter (OTC) setting. Nicorette®, in numerous well-controlled trials, has been shown to be safe and effective in helping individuals to quit smoking. The data contained within this supplement proves that Nicorette®, when utilized in an OTC naturalistic setting, has a similar efficacy and safety profile to that seen with average prescription usage. This supplement provides convincing evidence that Nicorette® can be adequately used by consumers without physician oversight.

Cigarettes and other tobacco products are widely available in this country. Cigarette smoking is the leading preventable cause of premature death and disease in the United States. Despite over 30 years of progress in reducing the prevalence of smoking in the U.S., approximately 46 million adult Americans continue to smoke. These 46 million adults constitute 25.7% of the adult population in the United States. If this smoking prevalence continues, it will result in hundreds of thousands of premature deaths annually, well into the next century. The public health implications of continuing our society's smoking pattern are significant. Besides the harm smoking causes to direct users, the EPA recently disclosed the potential harm to non-users, through second hand smoke. An important factor, not to be overlooked, is the emotional trauma upon family and friends who provide support for a smoker's eventual health problems. All of these well-known variables point to a large negative impact to our public health.

We know that many smokers recognize the health risks associated with smoking. This equates to a large number of smokers who attempt to quit annually. We also know that the majority of smokers who attempt to quit will not seek a physician's help in the quit attempt. Switching Nicorette® from prescription only to an OTC product is a way to increase access to a proven smoking cessation aid. The data presented in this supplement establish that the numbers of individuals successfully quitting will significantly increase by switching Nicorette® from Rx to OTC status.

Nicorette® is currently marketed in over 50 countries and has over 10 years of postmarketing experience in the U.S., and as much as 16 years of postmarketing experience in several other countries. Such broad safety experience has led to the availability of Nicorette® without prescription in 33 countries.

This supplement was developed through an interactive process with FDA, including both the Pilot Division and the OTC Office. There were several face-to-face meetings, numerous teleconferences and many FAXes involved in the submission's evolution.

The submission contains two readability studies and five label comprehension studies. The Nicorette® OTC intervention package consists of outer carton labeling, Nicorette® product, a User's Guide, and an audio cassette. Assessing label comprehension was an iterative process which began with readability studies in which adjustments were made to achieve the desired reading level. Likewise, studies to evaluate understandability and intention-to-act were conducted, labels were revised, and testing was carried out on revised labels to increase the level of understanding and the intention-to-act.

There are five usage studies included with this submission. Two of the usage studies involved Nicorette® OTC and evaluated nearly 3000 participants. One is a long term follow-up to the two simulated OTC use studies, and the other two involve real world use of prescription Nicorette®. In conjunction with the FDA, it was determined that the Nicorette® OTC usage studies would be designed as open-label, observational studies with no internal comparator, focusing on the ability of participants to self-select, to identify and deal with treatment-emergent events, and to establish an OTC quit rate. The OTC usage studies were as naturalistic as possible in simulating an OTC environment, both in their recruitment methods and in the conduct of the studies which allowed "all-comers" to self-select for treatment. Participants had minimal to no contact with the investigator and relied entirely on labeled instructions. The adequacy of the OTC labeling to allow appropriate self-selection, as well as the safe and effective use of Nicorette® was established. The study design agreed upon with FDA to establish the average prescription Nicorette® quit rate was a nationwide survey of patients who had filled Nicorette® prescriptions, ie "real world" use. Data derived from these studies establish comparable efficacy between Rx and OTC usage.

These supplements provide data which reiterate Nicorette®'s well-established efficacy and safety profile. In addition, this data package provides overwhelming evidence of Nicorette®'s suitability as an OTC product.

As we discussed in our teleconference with the Pilot Division on December 2, 1994, the full supplement is being sent to Nicorette® DS, NDA 20-066 (4 mg), and a cover letter only to Nicorette®, NDA 18-612 (2 mg). Also discussed was our agreement with Mr. Mike Jones concerning the requirement to pay only one user fee for these submissions. Included with both submissions is a User Fee Cover Sheet. A check has been submitted for one of the NDA supplements. On the other supplement's User Fee Cover Sheet, we have referenced the user fee ID number.

Pilot Drug Evaluation Staff, HFD-007  
December 9, 1994  
Page 3

Marion Merrell Dow Inc. certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b), in conjunction with this application.

SmithKline Beecham Consumer Healthcare has authorized Marion Merrell Dow Inc. to submit the attached supplemental NDA on their behalf and to communicate directly with FDA regarding this supplement to NDA 18-612 and NDA 20-066.

\_\_\_\_\_

\_\_\_\_\_

Please be advised that we consider all information in this submission to NDA 18-612 and NDA 20-066 confidential as provided in Title 21, Section 314.430 of the Code of Federal Regulations. We request that only specific authorization by Marion Merrell Dow Inc. will allow the Food and Drug Administration to reference this information.

If you have any questions, please contact Ms. Lorie Stewart at (816) 966-5170.

Sincerely,



Elaine Waller, PharmD  
Vice President, US Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297  
Expiration Date: November 30, 1996.

# USER FEE COVER SHEET

Reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and reviewing the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS  
Hubert H. Humphrey Building, Room 721-B  
200 Independence Avenue, S.W.  
Washington, DC 20201  
Attn: PRA

and to:

Office of Management and Budget  
Paperwork Reduction Project (0910-0297)  
Washington, DC 20503

Please DO NOT RETURN this form to either of these addresses.

**See Instructions on Reverse Before Completing This Form.**

**1. APPLICANT'S NAME AND ADDRESS**

MARION MERRELL DOW INC.  
P. O. Box 9627  
KANSAS CITY, MO 64134-0627

**2. USER FEE BILLING NAME, ADDRESS, AND CONTACT**

D. JEFFREY KEYSER  
MARION MERRELL DOW INC.  
10236 MARION PARK DRIVE  
KANSAS CITY, MO 64137

**3. TELEPHONE NUMBER (Include Area Code)**

(816) 966-5000

**4. PRODUCT NAME**

NICORETTE

**5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?**

YES

NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

**6. USER FEE I.D. NUMBER**

2698

**7. LICENSE NUMBER/NDA NUMBER**

N018612

**8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.**

A LARGE VOLUME PARENTERAL DRUG PRODUCT  
APPROVED BEFORE 9/1/92

THE APPLICATION IS SUBMITTED UNDER 505(b)(2)  
(See reverse before checking box.)

AN INSULIN PRODUCT SUBMITTED UNDER 506

**FOR BIOLOGICAL PRODUCTS ONLY**

WHOLE BLOOD OR BLOOD COMPONENT FOR  
TRANSFUSION

A CRUDE ALLERGENIC EXTRACT PRODUCT

BOVINE BLOOD PRODUCT FOR TOPICAL  
APPLICATION LICENSED BEFORE 9/1/92

AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT  
LICENSED UNDER 351 OF THE PHS ACT

**9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?**

YES

NO

(See reverse if answered YES)

**b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?**

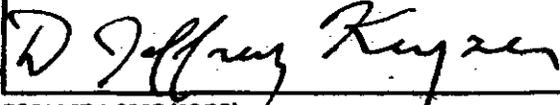
YES

NO

(See reverse if answered YES)

*This completed form must be signed and accompany each new drug or biologic product, original or supplement.*

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Director, U.S. Regulatory  
Affairs

DATE

December 9, 1994

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE  
(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.  
Expiration Date: April 30, 1994.  
See OMB Statement on Page 3.

FOR FDA USE ONLY

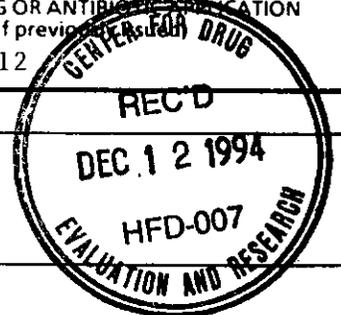
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT SmithKline Beecham Consumer Healthcare, L.P.	DATE OF SUBMISSION December 9, 1994
ADDRESS (Number, Street, City, State and Zip Code) 1500 Littleton Road Parsippany, NJ 07054	TELEPHONE NO. (Include Area Code) 201-631-8700
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previous application) 18-612

DRUG PRODUCT

ESTABLISHED NAME (e.g., USPIUSAN) nicotine polacrilex	PROPRIETARY NAME (If any) NICORETTE <sup>(R)</sup>
CODE NAME (If any) none	CHEMICAL NAME S-3-1(1-methyl-2-pyrrolidnyl)pyridine)
DOSAGE FORM chewing piece	ROUTE OF ADMINISTRATION oral
	STRENGTH(S) 2mg



PROPOSED INDICATIONS FOR USE  
Nicorette treatment is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. Nicorette treatment should be used as a part of a comprehensive behavioral smoking cessation program.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:  
NDA 20-066. NICORETTE 4 mg  
Merrell Dow Pharmaceuticals Inc.

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50)  THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
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TYPE SUBMISSION (Check one)

PRESUBMISSION  AN AMENDMENT TO A PENDING APPLICATION  SUPPLEMENTAL APPLICATION  
 ORIGINAL APPLICATION  RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS (Check one)

APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx)  APPLICATION FOR AN OVER - THE - COUNTER PRODUCT (OTC)

**Patent Certification - Nicorette® (Nicotine polacrilex)**

The undersigned certifies that a composition including nicotine polacrilex for providing a sense of smoking satisfaction without smoking is covered by the following expired U.S. patents. The compositions claimed in these patents are currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

- (1) U.S. Patent 3,901,248 expired August 26, 1992
- (2) U.S. Patent 3,845,217 expired October 29, 1991
- (3) U.S. Patent 3,877,468 expired April 15, 1992

The above patents which were assigned to Aktiebolaget Leo cover (1) a composition comprising a chewing gum base and nicotine held by a cation exchanger, (2) an identical composition plus a buffering agent and (3) nicotine in gum base.

Aktiebolaget Leo the holder of the above expired patents was a Swedish pharmaceutical company owned by Pharmacia AB.



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Lars Nilsson  
Vice President Regulatory Affairs  
Pharmacia Consumer Pharma

94 1130

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Date

**United States Patent** (19)

[11] **3,877,468**

**Lichtneckert et al.**

[45] **Apr. 15, 1975**

- [54] **CHEWABLE TOBACCO SUBSTITUTE COMPOSITION**
- [75] *Inventors:* **Stefan Lichtneckert; Claes Lundgren**, both of Lund; **Ove Ferno**, Halsingborg, all of Sweden
- [73] *Assignee:* **Aktiebolaget Leo**, Halsingborg, Sweden
- [22] *Filed:* **Jan. 28, 1974**
- [21] *Appl. No.:* **437,031**

**Related U.S. Application Data**

- [63] *Continuation of Ser. No. 164,105, July 19, 1971, abandoned.*

**Foreign Application Priority Data**

- July 22, 1970 **United Kingdom**..... 35605/70
- July 22, 1970 **United Kingdom**..... 35606/70

- [52] *U.S. Cl.*..... **131/2; 131/1**

- [51] *Int. Cl.*..... **A24b 15/00**
- [58] *Field of Search*..... **131/2, 15, 5, 17, 140-144, 131/16; 424/267, 266, 48, 79, 254, 48**

[56] **References Cited**

**UNITED STATES PATENTS**

904,521	11/1908	Ellis	131/2 X
2,341,986	2/1944	Hale	131/5 UX
2,600,700	6/1952	Smith	424/263
3,368,567	2/1968	Speer	131/17 R

*Primary Examiner*—Melvin D. Rein  
*Attorney, Agent, or Firm*—Gordon W. Huescher

[57] **ABSTRACT**

Chewable smoking substitute composition comprises at least about 40 percent by weight of a gum base and a tobacco alkaloid dispersed in said gum base in an amount sufficient to provide smoking satisfaction.

**3 Claims, No Drawings**

## CHEWABLE TOBACCO SUBSTITUTE COMPOSITION

This is a continuation of application Ser. No. 164,105, filed July 19, 1971, now abandoned.

### BACKGROUND OF THE INVENTION

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 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 snuffed are known but generally are not very satisfactory. Examples of such compositions are found in U.S. Pat. Nos. 875,026 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 mostly used and accepted today, the release of the alkaloid takes place very quickly. This is disadvantageous for two reasons: firstly, the alkaloid is released too quickly, higher blood concentrations of the alkaloid are produced than with ordinary smoking, and secondly, the substitute in question has too short an effect.

It has been our object to devise 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, lobeline, and the like, in the free base or pharmacologically acceptable acid addition salt form. Plant alkaloids of this type are obtainable from species of *Nicotiana* which is a source for nicotine and nor-nicotine, as well as species of *Lobelia* and *Lobeliaceae* (Indian tobacco) which are a source for lobeline.

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 also 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 using the substitute in question.
- d. The alkaloid released 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 one to excessive use of the substitute with less smoking satisfaction and thus lead to return to ordinary smoking.

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

### SUMMARY OF THE INVENTION

It has now been found that all of the foregoing advantages are realized if an amount effective to provide smoking satisfaction of a tobacco alkaloid, either as a base or in the form of a salt, is incorporated into chewable gum compositions having a relatively high gum base concentration. That is, contemplated are gum compositions having a gum base concentration of at least about 40 percent by weight or higher and containing the alkaloid dispersed therein. Preferably the smoking substitute composition of this invention is rendered acidic by the addition of a pharmacologically acceptable acidifying agent. In an alternate embodiment an alkaloid-regenerative adsorbent complex comprising the alkaloid or an acid addition salt thereof bound to or sorbed on a regenerative adsorbent such as finely divided silicic acid, amorphous silica, magnesium silicate, calcium silicate, kaolin, clays, crystalline aluminosilicates, macaloid bentonite, activated carbon, alumina, hydroxylapatite, and the like, is incorporated into the chewable gum base compositions having a relatively high gum base concentration. The alkaloid can be bound to the adsorbent either by absorption, adsorption, or both, thus the term "sorbed" as used herein is taken to mean either or both of the binding mechanisms. Also in this embodiment the smoking substitute composition preferably is acidic.

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 percent by weight to about 2 percent by weight, based on the weight of the gum base and calculated as the free base. Usually a chewable gum unit contains about 1 milligram to about 10 milligrams of an alkaloid. Preferably each gum unit contains from about 1 to about 5 milligrams of an alkaloid.

The total weight of a chewable gum unit can vary from about 0.5 to about 4 grams. The weight of each chewable gum unit is not critical for the purposes of the present invention but is chosen merely on the basis of convenience of manufacture, ease of dispensing, and, of course, ease of oral administration. The chewable gum unit can be in any desired form such as a stick, ball, or the like. Usually the weight of each gum unit is in the range from about 1 to about 3 grams.

### DESCRIPTION OF THE PREFERRED EMBODIMENTS

When the alkaloid is incorporated into the chewing gum mass in accordance with this invention it is possible to use a wide variety of chewing gum compositions as long as a relatively high gum base concentration is present.

Release rate of the alkaloid from the composition can be varied by varying the amount of alkaloid that is in-

corporated into a given quantity of gum, either separately or bound to a given quantity of the adsorbent. A relatively higher amount of 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 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 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 ("Vinnyapas"), "Dreyco" commercial gum base, polyvinyl esters, polyisobutylene and non-toxic butadiene-styrene 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, lanolin, hydrogenated cotton seed oil, hydrogenated coconut 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: cerelese, 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 about 40 to about 80 weight percent, preferably from about

50 to about 80 weight percent, and most preferably from about 60 to about 75 weight percent.

Powdered sugar, preferably powdered sorbitol, can be present in an amount in the range from about 15 to about 50 weight percent, preferably from about 16 to about 40 weight percent, and most preferably from about 20 to about 32 weight percent.

Corn syrup usually of about 41° to 46° Baume, preferably an about 70 percent aqueous solution of sorbitol, can be present in an amount in the range from about 4 to about 15 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 percent chewing gum base, preferably of synthetic origin (Preparation 1, 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 present invention can be formed simply by mixing the chewing gum with the alkaloid or alkaloid salt, preferably together with an excess of a suitable acidifying agent. Before adding any solid component, except for the gum base, it is desirable to grind and size the solid component first, to ensure a good distribution. The mixing is preferably conducted at a suitable elevated temperature depending upon the viscosity of chewing gum employed, since the increased temperature decreases the viscosity of the gum and thereby enables the alkaloid or alkaloid salt, together with an excess of acid, if desired, to be evenly and intimately distributed into the chewing gum.

As to the alkaloid-adsorbent complexes hereinabove mentioned, the content of nicotine or other alkaloid in the complex can range from about 2 to about 60 percent and preferably about 5 to about 35 percent by weight. The exact amount of the alkaloid or alkaloid mixtures bound to the adsorbent is determined principally by the conditions employed in formulating the compositions and, of course, by the type of adsorbent used.

The complex containing an alkaloid bound to the adsorbent 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. The complex also acts as a lubricant, thereby facilitating the mixture of the different ingredients into the gum mass. A homogeneous product is easily obtained in this manner.

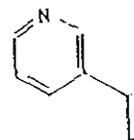
In compounding the present compositions with an alkaloid-adsorbent complex, if the complex is in the form of a relatively small particle size adsorbent in the first place, the complex can be mixed directly with the gum. If, however, the complex is in the form of a relatively coarse adsorbent, then it is desirable to grind and size the complex first. The complex particle size in the gum should be small enough not to cause damage to teeth during chewing, however.

In compounding the compositions with the various alkaloid-adsorbent complexes, singly or as admixtures of several alkaloids, the weight ratio of the complex to

the total weight of desired amount of between an upper specific to the form the alkaloid-adsorbent of about 0.1 to 10 of the gum, preferably about

Conveniently they are compounded of any additives flavors into the composition, such as a stabilizer and the gum base free from lumps are incorporated into the composition. The chemical properties of the gum base are biologically acceptable. An additional ingredient will be convenient, for instance, sulphuric acid or with the gum base, malic acid, it is the solid, powdered flavors, softer and well distributed and hardened before final wrapping. Rooms assure a "sweating" of enough heat to bring the additive temperature, together with it only when this minimizes your content:

As mentioned smoking substitute. This is of smoking because in an nicotine base



is shifted to nicotine absorption. Some of the the buccal found that it tion, to maintain at a pH range of about biologically: sition.

In one procedure utilizing an is only part is when incorporation of this

most preferably percent. sorbitol, can from about 15 to from about 16 to preferably from

46° Baume, pref- resolution of sorbi- the range from preferably from and most prefera- ercent.

exist, such as sug- tion of as much eferably of syn-

ne one hand the eginning of the econdary consi- simply by vary- ive formula. The ewing gum can s substances, as

it invention can g gum with the ther with an ex- ore adding any ase, it is desir- ent first, to en- preferably con- ture depend- oved, since the iscosity of the r alkaloid salt, d, to be even- ing gum.

es hereinabove her alkaloid in about 60 per- 35 percent by id or alkaloid rmined princ- mulating the e of adsorbent

und to the ad- cial unit. The dle and mini- anufacture of plex also acts tixture of the A homogene- mer.

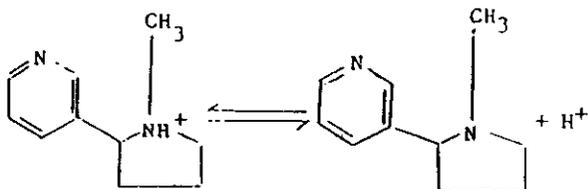
ns with an al- is in the form at in the first vith the gum. f a relatively rind and size e in the gum e to teeth

the various admixtures complex to

the total weight of the gum is not critical so long as the desired amount of the alkaloid is present, but varies between an upper and a lower most suitable range specific to the formulation used. Compositions wherein the alkaloid-adsorbent complex is present in an amount of about 0.1 to 10 percent by weight of the total weight of the gum, preferably about 0.2 to 5 percent, and most preferably about 0.5 to 2 percent, are suitable.

Conveniently compositions of the present invention are compounded 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 compounded in a suitable kettle, such as 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 acidifying agent such as a 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 acid with the solid, powdered part of sorbitol or sugar. Finally, flavours, 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 sufficient for mixing. The addition of sugar and syrup tends to lower the temperature, and the various alkaloids or alkaloid salts together with the flavouring agent if desired, are added only when the mixture has cooled sufficiently. This minimizes uncontrollable losses in alkaloid and/or flavour content to a marked degree.

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, thereby 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 upon chewing at a pH of less than about 7, and preferably in the range of about 5 to about 4, by incorporating a pharmacologically acceptable acidifying agent into the composition.

In one preferred embodiment of this invention when utilizing an alkaloid-adsorbent complex, the adsorbent is only partly loaded with nicotine or similar alkaloid when incorporated into a smoking substitute composition of this invention and is also loaded with a releas-

able or desorbable acid which serves as the acidifying agent. Upon chewing such a composition, the acid is also liberated from the adsorbent and pH of saliva at the chewing site is decreased. This decrease in pH influences, in turn, the acid-base equilibrium as set forth above. Similarly, it is possible to admix a fully nicotine-loaded adsorbent with a cation exchange resin in its acid form which releases hydrogen ions upon chewing to bring about the desired acidity at the chewing site, or to admix a fully nicotine-loaded adsorbent with a pharmacologically acceptable organic or inorganic acid, or to admix a fully nicotine-loaded adsorbent with a combination of a cation exchange resin in its acid form with a pharmacologically acceptable organic or inorganic salt.

In another preferred embodiment of this invention a cation exchanger in its ionic hydrogen form is introduced in the alkaloid-bearing gum composition to provide the desired acidity. 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. In still another preferred embodiment, the alkaloid-bearing gum composition is admixed with a pharmacologically acceptable organic or inorganic acid, or with a combination of a cation exchange resin in its acid form with a pharmacologically acceptable organic or inorganic salt.

The properties and characteristics of four cation exchange resins that we have found to be particularly suitable for use with the present invention are:

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

No	Type	Functional Groups
1	Weakly acidic, methacrylic Type	Carboxylic R COO H <sup>+</sup>
2	Weakly acidic, methacrylic Type	Carboxylic R COO H <sup>+</sup>
3	Strongly acidic, polystyrene Type	Sulfonic R SO <sub>3</sub> H <sup>+</sup>
4	Intermediate acidic, polystyrene Type	Phosphoric R PO <sub>3</sub> (H <sup>+</sup> ) <sub>2</sub>

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	Hydrogen	Same as (1.) above
3	Sodium converted to hydrogen	Not published, but, according to the manufacturer, this resin reacts as a "conventional gel porosity" resin.
4	Sodium converted to hydrogen	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	11.3

-Continued

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

No.	Particle size $\mu$	Percent External Water
1.	150-40	Maximum 5.0
2.	95% < 40	Maximum 5.0
3.	95% < 40	Maximum 10.0
4.	150-75	Maximum 4.0

The amount of pharmacologically acceptable acid present in any of the foregoing instances, can be in the range of about 1.5 to about 10 equivalents of acid per mole of the alkaloid base, preferably about 1.5 to about 6 equivalents of acid per mole of the alkaloid base, and most preferably about 2 to about 4 equivalents of acid per mole of the alkaloid base. Expressed in terms of the alkaloid present as a 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 of 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, phosphoric acid, and the like, as well as organic acids such as succinic acid, fumaric acid, glutaric acid, adipic acid, malic acid, tartaric acid, ascorbic acid, citric acid, mixtures of the aforesaid acids, and the like. 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.

Some Preparations and Examples are now given which are illustrative of the present invention.

#### PREPARATIONS OF THE INVENTION

<b>Preparation 1</b>	
Synthetic gum base	73.7 weight-percent
Powdered sorbitol	19.8 weight-percent
Sorbitol, 70 percent water solution	3.8 weight-percent
Glycerine	0.7 weight-percent
Flavouring oil	2.0 weight-percent
<b>Preparation 2</b>	
Synthetic gum base	55.0 weight-percent
Powdered sorbitol	34.0 weight-percent
Sorbitol, 70 percent water solution	8.9 weight-percent
Glycerine	0.6 weight-percent
Flavouring oil	1.5 weight-percent
<b>Preparation 3</b>	
Natural gum base	40.0 weight-percent
Powdered sugar	46.7 weight-percent
Corn syrup 45° Baume	11.7 weight-percent
Glycerine	0.5 weight-percent
Flavouring oil	1.1 weight-percent
<b>Preparation NOT According to the Invention</b>	
<b>Preparation 4</b>	
Natural gum base	22.0 weight-percent
Powdered sugar	64.0 weight-percent
Corn syrup 45° Baume	14.0 weight-percent

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

1000 Pieces of chewing gum each containing 2 mg of nicotine as base and an excess of acid (nicotine d-tartrate ( $C_{10}H_{14}N_2 \cdot 2\text{kaloid}$ ), present as  $C_4H_6O_6 \cdot 2 H_2O$ )

Chewing gum mass according to Preparation 1	1994 grams	Chewing gum mass - Nicotine, 100%	1000 Pieces of nicotine as base
Acid nicotine d-tartrate	6.16 grams	Nicotine, 100%	
		Nicotartrate, 100%	

#### EXAMPLE 2

1000 Pieces of chewing gum each containing 4 mg of nicotine as nicotine dihydrochloride ( $C_{10}H_{14}N_2 \cdot 2 HCl$ ).

Chewing gum mass according to Preparation 1	991 grams	Chewing gum mass - Nicotine, 100%	1000 Pieces of nicotine as base
Nicotine, 100% ( $C_{10}H_{14}N_2$ )	4.0 grams	Nicotine, 100%	/ mole of alkaloid
Hydrochloric acid, 38%	4.73 grams	Fumaric acid	

#### EXAMPLE 3

1000 Pieces of chewing gum each containing 4 mg of nicotine as neutral nicotine sulfate ( $(C_{10}H_{14}N_2)_2 \cdot H_2SO_4$ ) and an excess of acid (4.8 equivalents / mole of alkaloid salt), present as the cation exchanger Amberlite IRP 64M in hydrogen ionic form.

Chewing gum mass according to Preparation 1	983 grams	Chewing gum mass - Nicotine, 100%	1000 Pieces of nicotine as base
Nicotine, 100%	4.0 grams	Nicotine, 100%	/ mole of alkaloid
Sulfuric acid, 95%	1.28 grams	Hydrochloric acid	
Amberlite IRP 64M, 9.0 meq/gram	12.0 grams		

#### EXAMPLE 4

1000 Pieces of chewing gum each containing 3 mg of nicotine as neutral nicotine sulfate ( $(C_{10}H_{14}N_2)_2 \cdot H_2SO_4$ ) and an excess of acid (4.8 equivalents / mole of alkaloid salt), present as adipic acid.

Chewing gum mass according to Preparation 1	1490 grams	Chewing gum mass - Nicotine, 100%	1000 Pieces of nicotine as base and an excess present as acid
Nicotine, 100%	3.0 grams	Nicotine, 100%	
Sulfuric acid, 95%	0.96 grams	Lobeline, 100%	
Adipic acid	6.5 grams	Adipic acid	

#### EXAMPLE 5

1000 Pieces of chewing gum each containing 2 mg of nicotine as base and an excess of acid (5.8 equivalents / mole of alkaloid), present as the cation exchanger Amberlite IRP 69M converted to hydrogen ionic form.

Chewing gum mass according to Preparation 1	983 grams	Chewing gum mass - Nicotine, 100%	1000 Pieces of nicotine as base
Nicotine, 100%	2.0 grams	Nicotine, 100%	/ mole of alkaloid
Amberlite IRP 69M, 4.8 meq/gram	14.9 grams	Monosodium	

1 method described

EXAMPLE 6

1000 Pieces of chewing gum each containing 2 mg of nicotine as base together with 1 mg of nor-nicotine as base and an excess of acid (6 equivalents / mole of alkaloid), present as succinic acid.

1994 grams	Chewing gum mass according to Preparation 2	490 grams
6.16 grams	Nicotine, 100 %	2.0 grams
	Nor-nicotine, 100 % (C <sub>10</sub> H <sub>12</sub> N <sub>2</sub> )	1.0 grams

EXAMPLE 7

1000 Pieces of chewing gum each containing 1 mg of nicotine as base and an excess of acid (10 equivalents / mole of alkaloid), present as fumaric acid.

991 grams	Chewing gum mass according to Preparation 2	995 grams
4.0 grams	Nicotine, 100 %	1.0 grams
4.73 grams	Fumaric acid	3.58 grams

EXAMPLE 8

1000 Pieces of chewing gum each containing 5 mg of nicotine as base and an excess of acid (1.5 equivalents / mole of alkaloid), present as hydrochloric acid.

983 grams	Chewing gum mass according to Preparation 2	990 grams
4.0 grams	Nicotine, 100 %	5.0 grams
1.28 grams	Hydrochloric acid, 38 %	4.44 grams
12.0 grams		

EXAMPLE 9

1000 Pieces of chewing gum each containing 1 mg of nicotine as base together with 1 mg of lobeline as base and an excess of acid (8 equivalents / mole of alkaloid), present as adipic acid.

EXAMPLE 9, CONTINUED

1490 grams	Chewing gum mass according to Preparation 3	2993.0 grams
3.0 grams	Nicotine, 100 %	1.0 gram
0.96 grams	Lobeline, 100 % (C <sub>27</sub> H <sub>37</sub> NO <sub>2</sub> )	1.0 gram
6.5 grams	Adipic acid	5.34 grams

EXAMPLE 10

1000 Pieces of chewing gum each containing 3 mg of nicotine as base and an excess of acid (4 equivalents / mole of alkaloid), present as monosodium-citrate.

983 grams	Chewing gum mass according to Preparation 1	989.0 grams
2.0 grams	Nicotine, 100 %	3.0 grams
14.9 grams	Monosodiumcitrate	7.93 grams

EXAMPLE 11

1000 Pieces of chewing gum each containing 2 mg of nicotine as base and an excess of acid (3 equivalents / mole of alkaloid), present as monosodium phosphate

1996.0 grams	Chewing gum mass according to Preparation 1	1996.0 grams
2.0 grams	Nicotine, 100 %	2.0 grams
2.22 grams	Monosodium phosphate	2.22 grams

EXAMPLE 12

1000 Pieces of chewing gum each containing 3 mg of nor-nicotine as base and an excess of acid (4 equivalents / mole of alkaloid), present as malic acid.

1492.0 grams	Chewing gum mass according to Preparation 1	1492.0 grams
3.0 grams	Nor-nicotine, 100 %	3.0 grams
5.43 grams	Malic acid	5.43 grams

EXAMPLE 13

1000 Pieces of chewing gum each containing 2 mg of nicotine as base and an excess of acid (6 equivalents / mole of alkaloid), present as a mixture of malic acid and adipic acid

993.0 grams	Chewing gum mass according to Preparation 1	993.0 grams
2.0 grams	Nicotine, 100 %	2.0 grams
2.48 grams	Malic acid	2.48 grams
2.71 grams	Adipic acid	2.71 grams

EXAMPLE 14

1000 Pieces of chewing gum each containing 2 mg of lobeline as base and an excess of acid (8 equivalents / mole of alkaloid), present as monosodium fumarate.

1491.0 grams	Chewing gum mass according to Preparation 2	1491.0 grams
2.0 grams	Lobeline, 100 %	2.0 grams
6.54 grams	Monosodium fumarate	6.54 grams

CHEWING TESTS

The chewing gums in the following examples refer to a formulation prepared according to Preparation 1.

Each chewing gum unit or piece is composed of 1.0 gram of this mass.

EXAMPLE 15

Chewing gum containing a 10 percent complex is obtained from 3 mg of nicotine bound to silicic acid. Chewing gum mass according to Preparation 1, 1000 pieces of gum per 1970 grams of the mass. Silicic acid - 10 percent nicotine complex 30.0 grams.

EXAMPLE 16

Chewing gum containing a 10 percent complex, obtained from 2.5 mg. of nicotine bound to silicic acid, and likewise a 20 percent complex, obtained from 2.5 mg. of nicotine bound to silicic acid.

Chewing gum mass according to Preparation 2, 1000 pieces of gum per 1835 grams of the mass.

Silicic acid - 10 percent nicotine complex 25.0 grams.

Silicic acid - 20 percent nicotine complex 12.5 grams.

EXAMPLE 17

Chewing gum containing a 30 percent complex, obtained from 1 mg. of nicotine bound to silicic acid.

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

Silicic acid - 30 percent nicotine complex 3.33 grams.

EXAMPLE 18

Chewing gum containing a 30 percent complex, obtained from 2 mg of lobeline bound to silicic acid.

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

Silicic acid - 30 percent lobeline complex 6.67 grams.

EXAMPLE 19

Chewing gum containing a 20 percent complex, obtained from 1 mg of lobeline bound to silicic acid, and likewise a 35 percent complex obtained from 1 mg. of nicotine bound to silicic acid.

Chewing gum mass according to Preparation 1, 1000 pieces of gum per 1565 grams of the mass.

Silicic acid - 20 percent lobeline complex 5.0 grams.

Silicic acid - 35 percent nicotine complex 2.86 grams.

EXAMPLE 20

Chewing gum containing a 10 percent complex, obtained from 5 mg of nor-nicotine bound to silicic acid.

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

Silicic acid - 10 percent nor-nicotine complex 50.0 grams.

EXAMPLE 21

Chewing gum containing a 15 percent complex, obtained from 2 mg of nicotine bound to silicic acid, and likewise a 10 percent complex obtained from 1 mg. of nor-nicotine bound to silicic acid.

Chewing gum mass according to Preparation 1, 1000 pieces of gum per 2975 grams of the mass.

Silicic acid - 15 percent nicotine complex 13.33 grams.

grams.

Silicic acid - 10 percent nor-nicotine complex 10 grams.

Preparation of chewing gums containing the other various alkaloid absorbent complexes mentioned in the present application, either separately or mixture 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.

EXAMPLE 22

Chewing gum containing 4 mg of nicotine as neutral nicotine sulfate and an excess of acid (4.8 equivalent / mole of alkaloid salt), present as the cation exchange Amberlite IRP 64M in hydrogen ionic form.

Chewing time minutes	Mean value nicotine released mg
0	0
2	0.56
5	1.44
10	2.83
20	3.95

EXAMPLE 23

Chewing gum containing 4 mg of nicotine as nicotine dihydrochloride, i.e. 2 equivalents of acid / mole of alkaloid.

Chewing time minutes	Mean value nicotine released mg
0	0
2	0.48
5	1.34
10	2.68
20	3.88

We have found that it is possible to get a rather uniform extended release from a chewing gum upon chewing provided the alkaloid as such or as alkaloid salt is incorporated in a chewing gum formula containing a sufficiently high percentage of gum base. Among such chewing compositions those containing an excess of acid are more satisfactory as smoking substitutes, because they give a more pronounced "feeling of smoking".

Preparation of chewing gums containing other formulation variants mentioned in the present application can be 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.

Table I below is a compilation of experimental results showing the amount of nicotine released as a function of time.

TABLE I

Composition	RELEASED NICOTINE IN PERCENT BY WEIGHT AS A FUNCTION OF TIME						
	A1	A2	B1	B2	C1	C2	D
Time, min.							
2	9%	42%	15%	79%	14%	78%	12%
5	30%	58%	28%	87%	36%	87%	36%
10	62%	66%	59%	91%	71%	93%	67%
20	95%	88%	89%	100%	99%	100%	97%

A1 - Chewing gum containing nicotine base and high gum base.

A2 - Chewing gum containing nicotine base and low gum base.

B1 - Chewing gum mass having prepared in least amount of smoking.

B2 - Chewing gum containing nicotine as neutral nicotine sulfate.

C1 - Chewing gum containing nicotine as neutral nicotine sulfate and an excess of acid.

C2 - Chewing gum containing nicotine as neutral nicotine sulfate and an excess of acid.

D - Chewing gum containing nicotine as neutral nicotine sulfate.

From the experimental results it is apparent that the amount of nicotine released is essential for the effect of the salt. More pronounced feeling.

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FUNCTION OF TIME

C2	D
78%	12%
87%	36%
93%	67%
100%	97%

A1 - Chewing gum containing 4 milligrams of nicotine base and 1 gram chewing gum mass having a high gum base concentration, prepared in accordance with Preparation 1. Release brought about by chewing. Moderate feeling of smoking was observed.

A2 - Chewing gum containing 4 milligrams of nicotine base and 3 grams chewing gum mass having a low gum base concentration, prepared in accordance with Preparation 4. Release brought about by chewing. The observed initial nicotine release rate is too rapid for this composition to be suitable as a smoking substitute.

B1 - Chewing gum containing 4 milligrams of nicotine as neutral nicotine sulfate and 1 gram chewing gum mass having a high gum base concentration, prepared in accordance with Preparation 1. Release brought about by chewing. Moderate feeling of smoking was observed.

B2 - Chewing gum containing 4 milligrams of nicotine as neutral nicotine sulfate and 3 grams of chewing gum mass having a low gum base concentration, prepared in accordance with Preparation 4. Release brought about by chewing. The observed initial release rate is too rapid for this composition to be suitable as a smoking substitute.

C1 - Chewing gum containing 4 milligrams of nicotine as neutral nicotine sulfate and an excess of acid (4.8 equivalents of cation exchanger Amberlite IRP 64M in ionic hydrogen form per mole of the alkaloid salt) and 1 gram chewing gum mass having a high gum base concentration, prepared in accordance with Preparation 1. Release brought about by chewing. Very pronounced feeling of smoking was observed.

C2 - Chewing gum containing 4 milligrams of nicotine as neutral nicotine sulfate and an excess of acid (4.8 equivalents of cation exchanger Amberlite IRP 64M in ionic hydrogen form per mole of the alkaloid salt) and 3 grams chewing gum mass with low gum base concentration, prepared in accordance with Preparation 4. Release brought about by chewing. The observed initial release rate is too high for this composition to be suitable as a smoking substitute.

D - Chewing gum containing 4 milligrams of nicotine as nicotine dihydrochloride (i.e., containing 2 equivalents of acid per mole of alkaloid) and 1 gram chewing gum mass having a high gum base concentration, prepared in accordance with Preparation 1. Release brought about by chewing. Very pronounced feeling of smoking was observed.

From the data in the foregoing Table it is readily apparent that the presence of a high gum base concentration is essential for a satisfactory smoking composition which provides a substantially uniform, extended release of the alkaloid either in the form of a base or as a salt. Moreover, in compositions C1 and D the presence of an excess of an acid provided a more pronounced feeling of smoking.

DETERMINATION OF NICOTINE IN CHEWING 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 x 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  $E_{corr} = E_{min} - \frac{1}{2}(E_{min} + E_{282})$

$E^{corrected} (corr)$  has been determined to be 338

1cm

$$\frac{E_{corr} \times 1000 \times 250}{338 \times 100} = \text{mg nicotine chewing gum}$$

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

A detailed example of the preparation of a smoking substitute composition is given below.

EXAMPLE 24

About 400 grammes 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. 460 Grammes of powdered sugar (300 mesh sieve), 120 grammes Corn syrup 45° Baume, 5 grammes of glycerine, 10 grammes of flavouring oil, 5.3 grammes of nicotine sulfate and 12 grammes Amberlite IRP 64M (9.9 meq. acid/gram) 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° to 75°C, or lower.

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 grammes. In this Example, 1000 pieces, each weighing about one gram, 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 percent and the pieces are preferably stored at a temperature of 18° to 20°C and a relative humidity of 45 to 50 percent.

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

Some Preparations and Examples are now given exemplifying the use of an alkaloid-regenerative adsorbent complex. It should be realized from what has been said before that these compositions may not be performed but may in fact be formed simultaneously with the incorporation of the complex into the compositions. All percentages indicated are by weight.

Preparation 5: A nicotine-adsorbent complex containing 200 mg. of nicotine in 800 mg. of adsorbent in the dry state, i.e., a 20 percent compound (complex)

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

100.0 Grammes of silicic acid (Aerosil T.M.), 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 fully homogenized by stirring and afterwards dried to a weight of 125 grams at about 40°C in a drying cabinet provided with fan.

The nicotine-adsorbent complex thus obtained is then analyzed with reference to the nicotine content after careful blending and sieving through a 300 mesh sieve.

Preparation of other various alkaloid-adsorbent 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 adsorbents.

Table II below is a compilation of experimental results showing the amount of nicotine released as a function of time.

TABLE II

RELEASED NICOTINE IN PERCENT BY WEIGHT AS A FUNCTION OF TIME		
Composition	E1	E2
Time, min.		
2	18%	44%
5	47%	59%
10	71%	69%
20	94%	95%

E1 - Chewing gum containing 40 milligrams of silicic acid (Aerosil T.M.) complexed with nicotine base (10 weight percent nicotine) and 1 gram chewing gum mass having a high gum base concentration, prepared in accordance with Preparation 1. Release brought about by chewing. Uniform extended release and moderate feeling of smoking were observed.

E2 - Chewing gum containing 40 milligrams of silicic acid (Aerosil T.M.) complexed with nicotine base (10 weight percent nicotine) and 3 grammes chewing gum mass having a low gum base concentra-

tion, prepared in accordance with Preparation 4. Release brought about by chewing. The observed initial nicotine release rate is too rapid for this composition to be suitable as a smoking substitute.

Many regenerative adsorbents such as amorphous silica, silicic acid, clays, and the like are suitable for use in the preparation of the smoking substitutes. A detailed example of the preparation of one of the smoking substitutes is presented below

## EXAMPLE 18

A nicotine-silicic acid complex with Aerosil T.M. was prepared by the method described in Preparation 5, the resultant complex containing 10 percent nicotine.

434 Grammes natural gum base is put into a hot jacketed mixer fitted with stirrers. The mixer is heated by steam at about 15 lbs. per square 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 Grammes of powdered sugar (300 mesh sieve) and 276 grammes corn syrup 45° Baume 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° to 75°C.

A further 420 grammes of powdered sugar and 30 grammes of the nicotine-silicic acid 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 extruder 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 afterward 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 grammes. In this Example, 1000 pieces, each weighing two grammes, 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 percent and the pieces are preferably stored at a temperature of 18° to 20°C. and a relative humidity of 45 to 50 percent.

It will be illustrated that combination with other flavouring additives.

The foregoing illustrates other present in skilled in

We claim

1. A composition, having a high percentage of nicotine

1. a chewing gum

2. a chewing gum

where

A. the unit

gram

B. the post

and

weight

C. the amount

to

the base

D. the gum

light

ration 4. observed for this substitute. without silicic acid for use as a de-smoking

T.M. was on 5. the fine. hot jacket heated by irritants are gum preservative base. is turned the jacket to about 100 mesh volume are and the mixture to 75°C. for and 30 both 300 added as the kettle. so that the

and of this it is desirable before temperature mixture be practice the much by consistency

pieces of extruder heated by as a more heated by control. The with starch prevent it from lumps serve are preferred

in the conventional shape and usually weighs 1000 provided by procedure. under fairly wrapping a relative are preferred a relative

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

The foregoing discussion and examples are intended as illustrative and are not to be construed as limiting. Still other variations within the spirit and scope of the present invention will readily present themselves to one skilled in the art.

We claim:

1. A chewable "substitute for smoking" gum composition, having a "high percentage" of gum base, as said "high percentage" is hereinafter defined, comprising:

- 1. a chewing gum base and
- 2. nicotine, substantially uniformly distributed in said chewing gum base.

wherein:

- A. the composition is in the form of a chewable gum unit weighing in the range of about 0.5 to about 4 grams;
- B. the chewing gum base is present in said gum composition in a relatively high percentage, that is, an amount constituting at least about 40 percent by weight of said gum composition;
- C. the nicotine is present in said composition in an amount in the range of about 0.05 weight percent to about 2 weight percent based on the weight of the chewing gum base and calculated as the free base;
- D. the amount of nicotine distributed in said chewing gum base is in the range of about 1 to about 10 milligrams, such amount of nicotine approximating

the amount available upon smoking a smoking tobacco product;

E. the nicotine being present in said gum composition as a nicotine compound selected from the group consisting of

- a. a nicotine free base,
- b. a pharmacologically-acceptable salt of nicotine, and
- c. a nicotine-regenerative adsorbent complex comprising a compound selected from the group consisting of nicotine and a pharmacologically-acceptable salt of nicotine sorbed on a regenerative adsorbent;

F. said chewing gum composition when chewed releasing nicotine in small and reduced amounts within a period of the first few minutes of chewing, and

G. especially within the first ten minutes of chewing releasing the nicotine at a rate less than if the nicotine were present in an ordinary chewing gum composition, having a relatively low percentage of chewing gum base, that is, an amount constituting less than about 40 percent by weight of the gum composition.

2. The chewing gum composition of claim 1 wherein the amount of nicotine distributed in said chewing gum base is in the range of about 1 to about 5 milligrams, such amount of nicotine approximating that available upon smoking a cigarette.

3. The composition of claim 1, wherein the nicotine is present as a nicotine-regenerative adsorbent complex.

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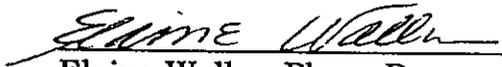
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## DEBARRMENT CERTIFICATION

Marion Merrell Dow Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b), in connection with this application.

  
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Elaine Waller, PharmD  
Vice President, US Regulatory Affairs

12.6.94.  
Date