



SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 12-132-681

TÍTULO SOLICITADO: PASTILLAS DE GELATINA BLANDA CON NICOTINA.

PUBLICACIÓN: Gaceta 651 de 31/08/2012, N° de publicación 1280.

PRIORIDAD: IN 452/MUM/2010 de 18/02/2010

SOLICITANTE: JATIN VASANT THAKKAR.

APODERADO: GERMAN MARIN RUALES

TRÁMITE: SUSTENTACIÓN DE OPOSICIÓN.

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito sustentar la oposición presentada, en los siguientes términos:

I. RATIFICACIÓN.

Comedidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

- En primer lugar, las reivindicaciones 5, 7 y 10 mencionan de nuevo el mismo excipiente ya mencionado en la respectiva reivindicación anterior (gelatina, glicerina y lecitina, respectivamente), es decir, replica innecesariamente contenido técnico, lo que contraviene lo relacionado a la concisión tal como lo expone el artículo 30 de la Decisión 486 de 2000 y el Manual Andino de Patentes (MAP), en consecuencia, el capítulo reivindicatorio de la solicitud en cuestión, no cumple con este requisito de concisión.
- En un segundo aspecto y teniendo en cuenta los excipientes que se han mencionado como plastificantes, edulcorantes, agentes liberadores (desintegrantes), conservantes, saborizantes en la reivindicación 1, así como en las reivindicaciones 4, 5, 6, 7, 8, 9, 10, 11, 12 y 13, carecen de nivel inventivo, puesto que todas estas funciones atribuidas a los correspondientes excipientes mencionados son convencionales y hacen parte del estado de la técnica, como cualquier persona versada en la formulación de productos farmacéuticos debe reconocer, en especial si se relacionan con procesos de fabricación de formulaciones farmacéuticas orales¹.
- La patente británica GB 2299756 publicada el 16 de octubre de 1996 y la patente española ES 2048510 publicada el 02 de septiembre de 1992 revelan la elaboración de formulaciones sólidas para la administración oral de nicotina, a través de formulaciones blandas compuestas principalmente de sustancias o agentes gelificantes (carragenano y gelatina) ya se habían utilizado con anterioridad; así mismo, otros compuestos tales como glicerina, sorbitol, almidón, sacarosa, dextrosa y agentes saborizantes ya se habían incluido en este tipo de formulaciones. También es relevante mencionar que dichas formulaciones se preparan a través del moldeo de la mezcla fundida de dichos componentes.
- Además de la demostrada ausencia de Novedad habida cuenta de las anterioridades mencionadas, la información recopilada en la totalidad de estos dos documentos resultan ser una clara guía para cualquier persona versada en la formulación de productos farmacéuticos, para la obtención de formulaciones del mismo tipo que las reivindicadas por la solicitud colombiana en trámite, por lo que es evidente la carencia de nivel inventivo.

III. COMPLEMENTO DE INFORMACIÓN.

Existen otras publicaciones que anticipan aspectos técnicos esenciales de la formulación colombiana en trámite, como por ejemplo la publicación internacional WO/1995/003050 publicada el 02 de febrero de 1995, la cual revela:

THE PRESENT INVENTION
This invention pertains to compositions and therapeutic methods for reducing the craving for nicotine and for smoking cessation. More particularly, this invention is directed to improved compositions of nicotine lozenges and therapeutic methods to provide periodic doses of nicotine to persons who are attempting to quit smoking.

(...)

Table I
Nonnutritive Sweeteners

Sweetener	Sweetness ¹	Sweetener	Sweetness ¹
Saccharin	400-500	Invert sugar	1.1-1.2
Cyclamate	30-40	Palantinose	0.4-0.5
Aspartame	100-200	Xylitol	1.0
Acesulfame	200	Sorbitol	0.5-0.6
Monellin	2500	Mannitol	0.4-0.6
Neohesperidine	1000	Maltitol	0.7-0.9
Palatinit	0.4-0.5	-	-

(...)

In addition, the lozenge may contain a flavorant, for example, a candy taste, such as chocolate, orange, vanilla, and the like; essential oils such as peppermint, spearmint and the like; or other flavor, such as aniseed, eucalyptus, 1-menthol, carvone, anethole and the like, to mask the taste of nicotine. See Hall et al. Food Technol. 14:488

(...)

Como se puede apreciar claramente, en esta anterioridad ya se habían revelado pastillas para administrar nicotina en combinación con los mismos agentes edulcorantes que los mencionados en la solicitud colombiana en cuestión, específicamente aspartame y sacarina (reivindicación 11), así como agentes saborizantes tales como vainilla y menta (reivindicación 13).

¹ Vila Jato J.L. Tecnología Farmacéutica. Volumen II. Páginas 91 a 105.

Por su parte la publicación internacional WO/2002/076211 publicada el 3 de octubre de 2002, revela:

The present invention relates to solid, oral dosage forms comprising a nicotine active, which are useful for reducing or preventing nicotine cravings by oral transmucosal delivery of the nicotine active. The invention also relates to methods of using such compositions for reducing or preventing nicotine cravings or tobacco usage.

(...)

A variety of nicotine actives are well known in the art and are commercially available. Specific examples of nicotine actives suitable for use in the present invention include nicotine oil, nicotine bitartrate, and nicotine complexed with cyclodextrin or polymer resins (e.g., nicotine polacrilex). Preferred nicotine actives are nicotine bitartrate, nicotine polacrilex, nicotine oil, and combinations thereof, especially nicotine bitartrate. The nicotine active may be used in one or more distinct physical forms well known in the art, including free base forms, encapsulated forms, ionized forms, and spray-dried forms.

(...)

High intensity sweeteners are useful for improving the sweetness profile of the composition, e.g., to provide a sweetness degree similar to table sugar. High intensity sweeteners are well known in the art and include soluble saccharin salts (e.g., sodium, calcium salts), the free acid form of saccharin, cyclamate salts, aspartame, Acesulfame-K (the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide), and sodium, ammonium, or calcium salts of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide. Preferred high intensity sweeteners are Acesulfame-K and aspartame, especially Acesulfame K. High intensity sweeteners, when used, typically comprise from about 0.001% to about 5% of the composition, more typically up to about 0.5% by weight of the composition.

(...)

Flavoring agents may be any natural or synthetic flavors such as known in the art, including mints (e.g., peppermint, spearmint), menthol, citrus (e.g., orange, lemon), other fruit flavors, vanilla, cinnamon, chocolate, and tobacco flavor. When used, the composition typically comprises a total of from about 0.5 to about 5 weight % of one or more flavorings.

Colorants include pigments, natural food colors and dyes which are suitable for food and drug applications, e.g., F.D.C. dyes and lakes. Colorants typically comprise from about 0.001% to about 0.05% of the composition.

(...)

En esta anterioridad se anticipan formulaciones sólidas para administración oral de nicotina que contienen dicho principio activo en diversas formas activas de la nicotina, específicamente nicotina polacrilex, aceite de nicotina, sales de nicotina, intercambiador de cationes de nicotina, complejos de inclusión de nicotina (reivindicación 2), así como agentes edulcorantes tales como aspartame y sacarina (reivindicación 11) y finalmente agentes saborizantes tales como menta, vainilla, sabores a fruta y cítricos (reivindicación 13).

En conclusión, la solicitud colombiana en trámite carece de novedad, en los aspectos mencionados, si se tiene en cuenta lo revelado en estas dos anterioridades.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

V. ANEXOS.

- ❖ Copia de la publicación internacional WO/1995/003050 publicada el 02 de febrero de 1995 páginas 1, 11 y 14.
- ❖ Copia de la publicación internacional WO/2002/076211 publicada el 3 de octubre de 2002 páginas 1, 5 y 7.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P. 44655 del C. S de la J.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US94/08160 (22) International Filing Date: 20 July 1994 (20.07.94) (30) Priority Data: 08/097,962 26 July 1993 (26.07.93) US (71) Applicant: PHARMETRIX CORPORATION [US/US]; 1330 O'Brien Drive, Menlo Park, CA 94025 (US). (72) Inventor: SANTUS, Gian, Carlo; Via Zuara, 8, I-Milan (IT). (74) Agents: SMITH, William, M. et al.; Townsend and Townsend Hourie and Crew, 20th floor, Steuart St. Tower, One Market Plaza, San Francisco, CA 94105 (US).			(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: IMPROVED NICOTINE LOZENGE AND THERAPEUTIC METHOD FOR SMOKING CESSATION (57) Abstract A method for smoking cessation therapy is described that is utilizing an improved nicotine lozenge to satisfy transient craving. The lozenge contains nicotine, a nonnutritive sweetener and an absorbent excipient.			

C. The Nonnutritive Sweetener

The lozenge will also contain a nonnutritive sweetener. Since nicotine has an acrid, burning taste, the choice of a sweetener for a nicotine lozenge can be critical, for many patients do not find the taste of nicotine palatable in lozenge form. Typically, a nonnutritive sweetener or combination of sweeteners will be utilized in the lozenges described herein.

A nonnutritive sweetener is a synthetic or natural sugar substitute whose sweetness is higher than or comparable to sucrose. Table I lists examples of nonnutritive sweeteners and their relative sweetness values.

Table I
Nonnutritive Sweeteners

Sweetener	Sweetness ¹	Sweetener	Sweetness ¹
Saccharin	400-500	Invert sugar	1.1-1.2
Cyclamate	30-40	Palantinos	0.4-0.5
Aspartame	100-200	Xylitol	1.0
Acesulfame	200	Sorbitol	0.5-0.6
Monellin	2500	Mannitol	0.4-0.6
Neohesperidine	1000	Maltitol	0.7-0.9
Palatinit	0.4-0.5	-	-

Thus, the nonnutritive sweetener should have a relative sweetness value between about 0.4 and 2500, as compared with sucrose, more typically between about 0.4 and 500, preferably between about 0.4 and 200, and more preferably, between about 0.4 and 2. See Makinen (1988) Oral Health 78:57-66, which is incorporated herein by reference.

In a preferred embodiment, the nonnutritive sweetener is also noncariogenic. The cariogenicity of a substance is dependent upon its susceptibility to fermentation by *Streptococcus mutans* and other oral microorganisms. Dental researchers have long recognized that fermentable sweeteners such as sucrose, glucose, starch, and corn syrup are

¹ Sucrose = 1.0

D. Other Ingredients

The lozenge preferably is a buffered formulation in order to aid in buccal absorption of nicotine. A preferred formulation is at a pH of about 6-11, and preferably at a pH of about 7-9. Preferred buffered formulations will include sodium carbonate, sodium bicarbonate, sodium phosphate, calcium carbonate, magnesium hydroxide, potassium hydroxide, magnesium carbonate, aluminum hydroxide, and other substances known to those skilled in the art, as well as combinations of the aforementioned substances. In a most preferred formulation, the lozenge will contain sodium carbonate and bicarbonate as buffering agents.

The buffering agent(s) should be present in an amount sufficient to adjust the pH of the lozenge to between 6 and 11, typically, between about 0.1 and 25 % by weight (wt%), preferably in an amount between about 0.1 and 10 wt%, and more preferably in an amount between about 0.1 and 5 wt%.

In addition, the lozenge may contain a flavorant, for example, a candy taste, such as chocolate, orange, vanilla, and the like; essential oils such as peppermint, spearmint and the like; or other flavor, such as aniseed, eucalyptus, 1-menthol, carvone, anethole and the like, to mask the taste of nicotine. See Hall et al. Food Technol. 14:488 (1960); 15:20 (1961); 19:151 (1965); 24:25 (1970); 26:35 (1972); 27:64 (1973); 27:56 (1973); 28:76 (1974); 29:70 (1974) 31:65 (1977); 32:60 (1978); and 33:65 (1979), each of which is incorporated herein by reference. It may also contain tobacco flavor in order to reproduce some of the sensation of smoking for the user. A small amount of colloidal silica (less than about 1 wt%) typically is added to tablets containing tobacco flavor to aid in manufacturing.

Magnesium stearate and/or hydrogenated vegetable oil may also be added to the formulation as lubricants. Typically, the lubricant will be present in an amount between about 0.1 and 25 wt%, preferably in an amount between about 0.1 and 10 wt%, and more preferably in an amount between about 0.1 and 5 wt%.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/076211 A1

(54) Title: NICOTINE-CONTAINING ORAL DOSAGE FORM

(57) Abstract: The present invention is directed to glassy matrix solid oral dosage forms useful for transmucosal oral administration of a nicotine active.

leaf, and other pharmacologically active compounds which are useful for reducing cravings for nicotine, such as lobeline. As used herein, "cravings for nicotine" include cravings associated with tobacco usage, such as smoking and chewing tobacco.

A variety of nicotine actives are well known in the art and are commercially available. Specific examples of nicotine actives suitable for use in the present invention include nicotine oil, nicotine bitartrate, and nicotine complexed with cyclodextrin or polymer resins (e.g., nicotine polacrilex). Preferred nicotine actives are nicotine bitartrate, nicotine polacrilex, nicotine oil, and combinations thereof, especially nicotine bitartrate. The nicotine active may be used in one or more distinct physical forms well known in the art, including free base forms, encapsulated forms, ionized forms, and spray-dried forms.

The oral dosage form comprises one or more nicotine actives in an amount effective to reduce nicotine cravings, preferably within one hour of starting oral administration. In preferred embodiments, the product configuration, including the amount of nicotine active, is effective to reduce nicotine cravings either rapidly (e.g., within about 10 minutes, preferably within about 5 minutes), over a prolonged period (e.g., at least about 1 hour, preferably at least about 2 hours), or both, preferably both. Such combined rapid and prolonged craving relief may result from either the nicotine active per se or a combination of the nicotine active with other means which reduce acute or extended nicotine cravings (e.g., non-pharmacological sensory signals (including taste, tactile, scent signals) provided by inert components, such as flavor, cooling, tingling, effervescence). For example, the composition may comprise one or more flavors to provide rapid craving relief and an amount of nicotine active effective to provide relief of prolonged cravings.

In general, the amount of nicotine active may vary depending on the recommended or permitted therapeutic dosage for the particular nicotine active. Such dosages are known or ascertainable by conventional methods by those skilled in the medical arts. The composition preferably comprises from about 0.5 mg to about 5 mg of nicotine active per unit dosage form, more preferably from about 1 to about 4 mg nicotine active per unit dosage form.

The nicotine active is preferably substantially contained in the glassy matrix, and may be uniformly distributed throughout the matrix or distributed in one or more regions of the matrix.

The oral dosage form of the present invention may contain one or more optional ingredients, including ingredients such as are known in the art, e.g., buffers, flavorings, sugars, other sugar alcohols, high intensity sweeteners, colorants, vitamins, and antioxidants. Such optional ingredients may be used as adjuvants or as co-carriers for the

nicotine active and optional components (e.g., sugars and sugar alcohols may be a co-carrier).

One or more buffer materials are especially desirable to facilitate transmucosal absorption of nicotine actives such as nicotine and nicotine derivatives. The buffer provides an alkaline mouth saliva pH that tends to enhance transmucosal absorption of such nicotine actives. Suitable buffer materials include inorganic or organic bases which have the capability to provide a mouth saliva pH of from above 7.0 to about 12.0, preferably above 7.0 to about 11.0, more preferably from about 7.5 to about 10.0, also about 7.5 to about 9.0. Suitable buffer materials include sodium carbonate, sodium bicarbonate, calcium carbonate, potassium carbonate, potassium bicarbonate, sodium phosphate dibasic, sodium phosphate tribasic, potassium phosphate dibasic and potassium phosphate tribasic. The buffer preferably comprises sodium carbonate, potassium carbonate, or a mixture thereof.

Preferably sufficient buffer is used such that the mouth saliva pH becomes and remains alkaline while the oral dosage form is held in the mouth during oral administration. When used, the composition generally comprises from about 0.2% to about 5.0 % (e.g., about 0.5% to about 1.5%) buffer.

One or more sugars or other sugar alcohols may be used, e.g., as bulking agents. It has been found that such other sugar components may reduce the processing temperature required to form the oral dosage form, thereby tending to maintain stability of nicotine actives such as nicotine and its derivatives, and to increase the cost effectiveness of the process. Suitable other sugar components include sucrose, sorbitol, and xylitol, and in a preferred embodiment is sorbitol.

It is preferred that the oral dosage form is itself substantially non-hygroscopic and glassy. Therefore, the type and amount of optional other sugar components will preferably be selected such that the oral dosage form is substantially non-hygroscopic and glassy. In preferred embodiments, the oral dosage form absorbs a maximum of about 30% water by weight, more preferably a maximum of about 20% water by weight, even more preferably a maximum of about 10% by weight (e.g., up to about 8% by weight), still more preferably a maximum of about 5% by weight (especially a maximum of about 1-2% by weight), upon exposure to conditions of 25C/80% rh for a period of 2 weeks. Typically the oral dosage form will comprise from 0% to about 20%, e.g., from about 1% to about 20% or from about 10% to about 20% of such other sugar components, inclusive of any such components that may be present in the required sugar alcohol component. The composition may comprise higher levels of such other sugar components, provided that the matrix structure and hygroscopicity are acceptable.

High intensity sweeteners are useful for improving the sweetness profile of the composition, e.g., to provide a sweetness degree similar to table sugar. High intensity sweeteners are well known in the art and include soluble saccharin salts (e.g., sodium, calcium salts), the free acid form of saccharin, cyclamate salts, aspartame, Acesulfame-K (the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide), and sodium, ammonium, or calcium salts of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide. Preferred high intensity sweeteners are Acesulfame-K and aspartame, especially Acesulfame K. High intensity sweeteners, when used, typically comprise from about 0.001% to about 5% of the composition, more typically up to about 0.5% by weight of the composition.

Flavoring agents may be any natural or synthetic flavors such as known in the art, including mints (e.g., peppermint, spearmint), menthol, citrus (e.g., orange, lemon), other fruit flavors, vanilla, cinnamon, chocolate, and tobacco flavor. When used, the composition typically comprises a total of from about 0.5 to about 5 weight % of one or more flavorings.

Colorants include pigments, natural food colors and dyes which are suitable for food and drug applications, e.g., F.D.C. dyes and lakes. Colorants typically comprise from about 0.001% to about 0.05% of the composition.

Vitamins such as vitamin C and E may be included.

Small amounts of vegetable oils, e.g., sesame oil, may be added to the composition as a processing aid, more particularly as an anti-adhesive agent/lubricant to prevent the composition from sticking to equipment, molds, and the like. Typically up to about 1% of such oils, based on the weight of the composition, may be used.

Small amounts of citric acid may be included, e.g., to prevent discoloration of the composition during processing.

In further embodiments, the oral dosage form of the present invention may be substantially free or essentially free of water-soluble gelling agents (e.g., guar gum, gum arabic, and the like), and/or substantially free or essentially free of zinc. In this respect, "essentially free" means such ingredients are not intentionally added.

The solid oral dosage forms may also contain pharmaceutically acceptable polymers and binders and/or mixtures of such polymers and binders. Such polymers and binders include, but are not limited to:

Homo- or copolymers of N-vinylpyrrolidone such as polyvinylpyrrolidone (PVP), copolymers of N-vinylpyrrolidone with vinyl esters, especially with vinyl acetate, or also with vinyl propionate. Copolymers of vinyl acetate and crotonic acid, partly saponified polyvinyl acetate or polyvinyl alcohol;