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<p>(21) International Application Number: PCT/SE90/00848 (22) International Filing Date: 18 December 1990 (18.12.90) (30) Priority data: 8904295-6 21 December 1989 (21.12.89) SE (71) Applicant (for all designated States except US): PHARMACIA AB [SE/SE]; S-751 82 Uppsala (SE). (72) Inventors; and (75) Inventors/Applicants (for US only) : CARLSSON, Thommy [SE/SE]; Piteågatan 16, S-252 52 Helsingborg (SE). ANDERSSON, Sven, Börje [SE/SE]; Tuvegatan 14, S-260 35 Ödåkra (SE). (74) Agent: THYLÉN, Eva; Pharmacia Leo Therapeutics AB, Box 941, S-211 09 Helsingborg (SE).</p>		<p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i></p>
<p>(54) Title: SMOKING SUBSTITUTE</p> <p>(57) Abstract</p> <p>The present invention concerns a smoking substitute composition wherein nicotin is the form of an inclusion complex between nicotine and a cyclodextrin compound.</p>		

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SMOKING SUBSTITUTE

5 In the US Surgeon General's 1988 report on The Health Consequences of Smoking, it was estimated that in the US alone about 300.000 deaths are caused each year by diseases related to cigarette smoking. In fact, excessive smoking is now recognized as one of the major health problems throughout the world. The most advantageous thing a heavy smoker can do is, therefore, to reduce
10 or preferably even stop smoking completely. Experience shows, however, that most smokers find this extremely difficult. It is generally accepted that this difficulty results from the fact that heavy smokers are dependent on nicotine, which is considered to be one of the risk factors in tobacco smoke. The most important risk factors, however, are substances which are formed during the combustion of tobacco, such as carbon monoxide, tar
15 products, aldehydes, and hydrocyanic acid.

20 One way to reduce smoking is to provide nicotine in a form or manner other than by smoking and some products have been developed to this end. The most successful product, which is used as a smoking substitute and/or as a smoking cessation aid and which is based on nicotine, is the chewing gum Nicorette[®]. To date this product is the only form of nicotine replacement which has been
25 approved by the Food and Drug Administration (FDA). Nicorette[®] has been on the market in about thirty countries for several years. In this chewing gum the nicotine is present in the form of a complex with an insoluble cation-exchanger (polacrilex) which is dispersed in a gum base. A buffering agent is also included in
30 this composition. Patents related to this product are the US Patents 3,877,468, 3,901,248 and 3,845,217.

Another product within this field is Favor[®] which was on the US market for approximately 18 months but which had to be withdrawn as it did not fulfil the requirements set up by the Food and Drug Administration. This product, which is covered by the US patents
5 4,284,089 and 4,800,903, is a nicotine inhalation device consisting of an elongated tube, in which a porous polymer plug including nicotine free base, is arranged. The main problem with this nicotine delivery system concerned the volatility of the nicotine free base which very rapidly disappeared from the system. It has
10 been estimated that the shelf-life of the unrefrigerated vapor inhalor was approximately 1 month.

A product which has not yet been approved by the health authorities but which is now undergoing clinical trials is a nicotine
15 nasal solution of the type disclosed in the US 4,579,858. This product is also based on the use of nicotine free base.

Other compositions for nasal use is disclosed in the US
4,655,231. According to this patent the composition is based on
20 water soluble nicotine salts of organic acids, preferably oxalic acid. To the best of our knowledge no clinical studies have been performed with these compositions. It can be assumed, however, that when the salt dissociates in the nasal cavity, the acid moiety will increase the irritant sensation on the mucous membran
25 originating from the nicotine base formed.

The main problems with products based on nicotine free base originate from the volatility of the nicotine, the irritant sensation of the mucous membranes, and the decomposition of nicotine in
30 the presence of oxygen. To some extent these problems are also met with when nicotine is used in the form of a complex with an insoluble cation-exchanger resin as in the Nicorette[®] product, which was developed by our company and from which we have by now a broad experience. It should also be born in mind that the nicotine is released from the nicotine resin only after extensive
35 chewing.

The present invention concerns compositions to be used as a smoking substitute and/or as a smoking cessation aid comprising nicotine in the form of an inclusion complex formed between nicotine and a cyclo compound, preferably a cyclized polysaccharide, and a pharmaceutically acceptable carrier or adjuvant.

At present we consider β -cyclodextrin to be the most preferred cyclo compound, but other cyclodextrins such as α - and γ -cyclodextrin can also be used. Also derivatives of cyclodextrines are of interest, e.g. trimethyl- β -cyclodextrin, dimethyl- β -cyclodextrin, hydroxyethyl- β -cyclodextrin and hydroxypropyl- β -cyclodextrin.

The compositions of the invention are distinguished by several desirable characteristics making them useful for different types of pharmaceutically acceptable preparations, such as tablets, capsuls, powders, chewing gums. These characteristics include improved stability, improved taste, good bioavailability, pH independent release, reduced irritant sensation.

A preferred embodiment of the composition according to the invention is a tablet for sublingual or buccal administration. In this composition the nicotine in the form of the inclusion complex may be present in an amount of 0,05 - 10 %, and the rest, apart from a minor amount of a conventional lubricant, such as magnesium stearate, is a water-soluble, direct compressible excipient. This excipient should be palatable or tasteless and water soluble and accepted for use in pharmaceutical preparations or as a food additive. With excipients tested so far good results have been obtained with β -cyclodextrin, lactos, sorbitol and mannitol. A special advantage is that this tablet can be very easily prepared with a minimum of additives. Our experiments have shown that the stability of nicotine inclusion complex can be decreased by the addition of common additives and, so far, the best stability re-

sults have been obtained with preparations including only the complex, an excipient and a lubricant. Optionally also a flavouring agent could be present. In comparison with the Nicorette® chewing gum it has been found that both the taste and the irri-
5 tant sensation in the throat are diminished in the sublingual tablet according to the invention. Another interesting finding according to preliminary experiments is that no buffering agent is needed contrary to what could be expected from the experience with the chewing gum, Nicorette®, wherein a buffering agent is
10 necessary.

The cyclodextrin inclusion complexes can be prepared according to methods well known to a person skilled in the art. The most com-
15 mon procedures comprise stirring or shaking of an aqueous solution of the particular cyclodextrin with the nicotine. The reaction is preferably carried out in a common solvent like water. After an equilibrium is reached, the solvent can be removed by filtration. The cyclodextrin-nicotine complex is then mixed with the selected excipients and compressed into tablets or for-
20 mulated to a powder for nasal administration. It can also be dispersed in a gum-matrix for the preparation of a chewing gum.

Of particular value is the improved stability as stability problems with nicotine pharmaceutical preparations are very usual
25 and difficult to solve. The stability can be divided into three categories:

- a) improved stability as regards evaporation (reduced volatility)
- b) improved stability as regards decomposition through oxidation
30 (resistance to oxidation) and
- c) improved stability to light, which is related to b) as oxidation of nicotine is believed to take place through radical induced reaction. Such reactions are often catalyzed by light
35 radiation.

According to the invention all these three categories of stability are considerably improved if the complexes according to the invention are used instead of nicotine free base.

When in proper environment (e.g. saliva in the mouth) the inclusion complex of the invention permits release of nicotine. Furthermore, the complexes are easy to handle and can readily be transferred to different pharmaceutical preparations, to which different and desirable release profiles can be imparted.

The invention is further illustrated by the following examples which should not be construed as limiting the invention:

10 Example 1

Preparation of inclusion complex of β -cyclodextrin (β -CD) and nicotine.

15 This complex, which is previously known from Anal. Chem. 1984, 56 2827-2830, was prepared as follows:

100 g of water was heated to 75°C. 25 g of β -CD were added and dissolved while stirring the solution. 3,5 ml of nicotine (obtained from Eastman Kodak) were added. The mixture was stirred for about 4 h at ambient temperature. The obtained mixture was filtered and dried in a drying oven at 35°C.

25 Example 2

1.500 tablets having the following composition were prepared.

Composition per tablet:

30	B-CD-nicotine	34,8 mg (respond to 4 mg nicotine)
	Sorbitol powder	500 mg
	PEG 6000	100 mg
	Sodium carbonate	24 mg
35	Ethyl cellulose N-7	12 mg
	Silicone oil 300/350 cSt	1,27 mg

Sorbitol, PEG-6000, β -CD nicotincomplex and sodium carbonate were sieved and mixed.

The silicone oil was added to the ethyl cellulose dissolved in ethanol while stirring.

5 The powder was moistened with the ethanol solution and the obtained product was dried at 40°C until the ethanol had evaporated and a granulate was obtained. This granulate was sieved and 0,5 % Mg stearate was added. The mixture was agitated for 3 minutes, and compressed to tablets.

10

Example 3

1.500 tablets having the following composition were prepared.

15 Composition per tablet:

β-CD-nicotine	34,8 mg (respond to 4 mg nicotine)
Sorbitol powder	500 mg
PEG 6000	100 mg
20 Ethyl cellulose N-7	12 mg
Silicone oil 300/350 cSt	1,27 mg

Sorbitol, PEG-6000, β-CD nicotincomplex were sieved and mixed.

25 The silicone oil was added to the ethyl cellulose dissolved in ethanol while stirring.

30 The powder was moistened with the ethanol solution and the obtained product was dried at 40°C until the ethanol had evaporated and a granulate was obtained. This granulate was sieved and 0,5 % Mg stearate was added. The mixture was agitated and compressed to tablets.

35

Example 4

Tablets were prepared from the following ingredients:

5	β -CD-nicotine	43,5 g (respond to 2 mg nicotine)
	β -CD	179,2 g
	Mg stearate	2,3 g
	2500 tablets weigh	225,0 g

10 All the ingredients were placed in an environment with low humidity for more than 24 h. The ingredients were sieved through sieve 1,0 and mixed in a double cone mixer for 5 minutes and compressed to tablets.

15 Example 5

Tablets were prepared in essentially the same way as described in Example 4 from the following ingredients:

20	β -CD-nicotine	87,0 g (respond to 2 g nicotine)
	Lactose	358,4 g
	Mg stearate	4,5 g
	5000 tablets weigh	450,0 g

25 Example 6

Tablets were prepared in essentially the same way as described in example 4 from the following ingredients:

30	β -CD-nicotine	89,5 g (respond to 2 g nicotine)
	Sorbitol	356,0 g
	Mg stearate	4,5 g
	5000 tablets weigh	450,0 g

35

Example 7

Tablets were prepared in essentially the same way as described in example 4 from the following ingredients:

5

β -CD-nicotine	87,0 g (respond to 2 mg nicotine)
Starch (Sta Rx 1500)	358,0 g
Mg stearate	4,5 g
5000 tablets weigh	450,0 g

10

Example 8

Tablets were prepared in essentially the same way as described in example 4 from the following ingredients:

15

β -CD-nicotine	89,5 g (respond to 2 mg nicotine)
Mannit	356,0 g
Mg stearate	4,5 g
5000 tablets weigh	450,0 g

20

Example 9

Tablets were prepared in essentially the same way as described in example 4 from the following ingredients:

25

β -CD-nicotine	87,0 g (respond to 2 mg nicotine)
Avicel pH 101	358,4 g
Mg stearate	4,5 g
5000 tablets weigh	450,0 g

30

Experiment 1

Tablets prepared according to the above examples were stored for approximately 1 month in an environment having the temperature 40°C.

35

The following observations on the tablets were made:

Tablet prepared
according to

5	<u>Example No</u>	<u>Test time (days)</u>	<u>Appearance</u>
	2	32	yellow-brown spots
	3	32	"
	4	32	without remark
10	5	38	"
	7	34	"
	8	34	"
	9	38	"

15 Preliminary results also indicated that the loss of nicotine from
the tablets was quite small or negligible. Most nicotine had disap-
peared from the tablets prepared according to the Examples 2 and
3. No increase of oxidation products of nicotine, such as cotini-
20 ne, myosmine, nicotine-N-oxide, were found in the tablets after
storage for one month at 40°C.

Experiment 2

25 In this experiment nicotine- β -cyclodextrin powder was placed in a
porous bag of synthetic material (type tea bag) in an amount cor-
responding to 6 mg nicotine. A bag was placed in the mouth of a
person and the nicotine plasma level was measured. Figure 1 dis-
closes the average nicotine plasma level of four persons versus
30 time.

30

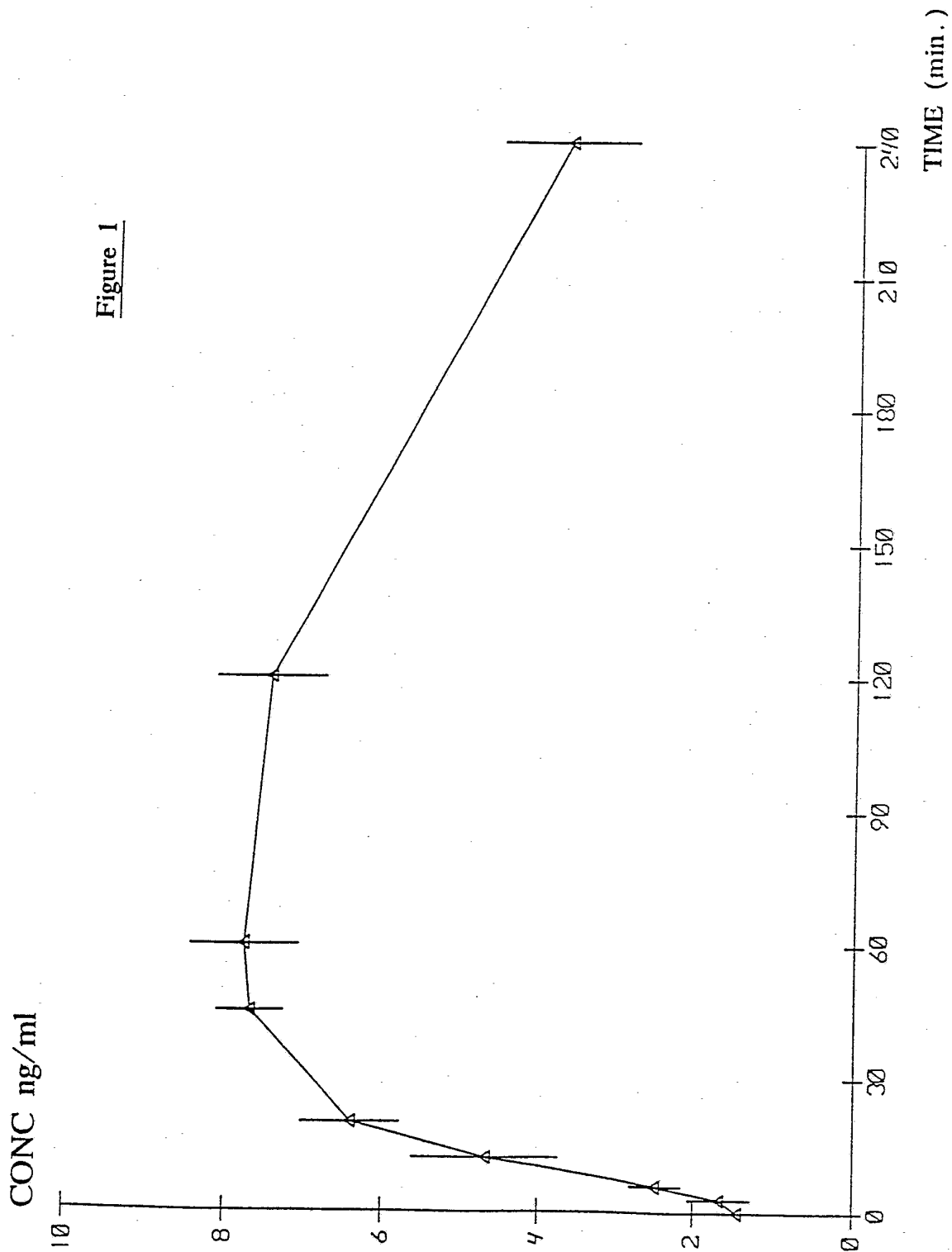
35

Claims

- 5 1. A smoking substitute composition comprising nicotine in the form of an inclusion complex of nicotine and a cyclodextrin compound.
- 10 2. A composition according to claim 1 characterized in that it also comprises excipients accepted for pharmaceutical use or as food additive.
- 15 3. A composition according to claim 2 for sublingual or buccal administration characterized in that the excipient is a direct compressible, water soluble substance.
- 20 4. A composition according to claim 3 characterized in that the excipient is selected from the group consisting of lactose, cyclodextrin, sorbitol and mannitol.
- 25 5. A composition according to any of the preceding claims essentially consisting of 0,1 - 10 % (w/w) nicotine in the form of a cyclodextrin complex, 0,05 - 3 % lubricant and a remaining part of lactose, cyclodextrin, sorbitol or mannitol.
- 30 6. A composition according to any of the claims 1 or 2 for nasal administration.
- 35 7. A composition according to claim 6 wherein the composition is in the form of a powder.
8. A chewing composition according to claim 1 or 2 wherein the inclusion complex is dispersed in a gum matrix.

1/1

Figure 1



INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 90/00848

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC5: A 61 K 31/465, 31/715, A 24 B 15/16		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC5	A 61 K; A 24 B	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched ⁸		
SE,DK,FI,NO classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP, A2, 0148749 (ADVANCED TOBACCO PRODUCTS, INC.) 17 July 1985, see page 10, line 7 - line 20; claims 9-10 and the examples --	1
Y	FR, A, 2275161 (KICHI ARAKAWA) 16 January 1976, see page 2, line 11 - page 3, line 21; page 5, line 16 - page 6, line 16 --	1-3
Y	FR, A, 2608156 (G. LEJEUNE) 17 June 1988, see page 2, line 1 - line 16 --	1-3,8
Y	GB, A, 2142822 (A.S.W. SHAW) 30 January 1985, see the whole document --	1-5,8
<p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
20th March 1991	1991 -03- 21	
International Searching Authority	Signature of Authorized Officer	
SWEDISH PATENT OFFICE	<i>Eva Johansson</i> Eva Johansson	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	US, A, 3845217 (O.B. FERNO AND C.B.I. OHLSSON) 29 October 1974, see column 3, line 21 - line 41; column 4, line 52 - line 59 --	1-5,8
Y	Analytical Chemistry, Vol. 56, No. 14, 1984 S.M. Han et al: "Solute-induced circular dichroism: drug discrimination by cyclodextrin", see page 2827 - page 2830 especially p. 2829 (Table I) --	1-3
Y	Chemistry in Britain, Vol. 23, No. 5, 1987 J.S. Pagington: "Beta-cyclodextrin: the success of molecular inclusion", see page 455 - page 458 especially p. 455 (Complex stability) and p. 456 (Pharmaceutical applications) -- -----	1-4

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 90/00848**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on **91-02-28**.
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		SE-B-C- 403702	78-09-04