

Señor

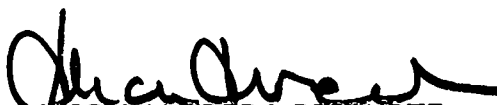
SUPERINTENDENTE DELEGADO PARA LA PROPIEDAD INDUSTRIAL
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-GRUNENTHAL GmbH.-Expediente número
00-074.927.-

1. Me refiero al asunto de la referencia.
2. Por medio del presente, atentamente me permito manifestar que hubo un **cambio** de apoderado para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **GRUNENTHAL GmbH**.
3. En consecuencia, atentamente solicito a ese Despacho reconocirme personería en este asunto, de conformidad con la sustitución de poder adjunta, otorgada a favor de la SUSCRITA.
4. Por lo tanto, ruego a usted notificarme de las providencias expedidas dentro de este expediente y notificadas al anterior apoderado, que actualmente se encuentran pendientes de cumplimiento o de respuesta.
5. Solicito a ese Despacho proceder de conformidad.

Atentamente,


ALICIA LLOREDA RICAURTE

T.P. 53.215

Código 231

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Señor
 SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
 DIVISION DE NUEVAS CREACIONES
 E. _____ S. _____ D. _____

Ref: P1.- GRUNENTHAL GmbH- Expediente No.00-074.927-

Yo, **JOSE ANTONIO LLOREDA**, mayor de edad y vecino de esta ciudad, abogado titulado e inscrito, identificado como aparece al pie de mi firma, actuando en mi carácter de Representante Legal en Bogotá para asuntos relacionados con la propiedad industrial de **GRUNENTHAL GmbH**, sociedad organizada y existente de conformidad con las leyes de Alemania, domiciliada en Aachen, Alemania, tal y como consta en este expediente, atentamente manifiesto a usted que **SUSTITUYO** el poder a mi conferido a la doctora **ALICIA LLOREDA RICAURTE**, abogada titulada e inscrita, identificada con la cédula de ciudadanía No. 39.690.713 de Usaquén y Tarjeta Profesional N° 53.215 para que continúe representando a la mencionada sociedad en el expediente de la referencia.

De conformidad con el artículo 66 del C.P.C., manifiesto bajo la gravedad de juramento que los demás apoderados citados en el documento otorgado a mi favor no desean ejercer el poder a ellos conferido.

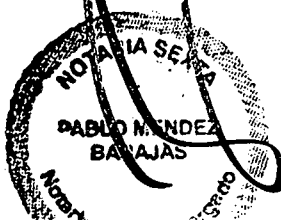
El mencionado apoderado tendrá las mismas facultades a mi conferidas, en especial, renunciar, recibir, sustituir, asistir, presentar recursos, conciliar, transigir, y en fin, para todo lo que se encamine a la correcta defensa de los intereses de la sociedad en cuyo nombre hablo.

Ante mí **PABLO MENDEZ BARAJAS**
 NOTARIO SEXTO(E) DEL CIRCUITO DE BOGOTÁ
 Atentamente, **25-4-2004**

Comparecieron: **Jose Antonio Lloreda**
Lloreda **JOSE ANTONIO LLOREDA**
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quien (es) es (es) (es) (es) C.C.
#17.159.681
T.P. 10784
 y declaró (es) (es) (es) (es) que aparece(n)
 en el presente documento (es) (es) (es) (es) cuya (es) y
 que el (es) (es) (es) (es) es (es) cierto.
 En fe de lo cual, para esta diligencia y se imprime
 el presente documento.

JOSE ANTONIO LLOREDA
 C.C. No. 17.159.681 de Bogotá



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3,652,589

1-(m-SUBSTITUTED PHENYL)-2-AMINOMETHYL CYCLOHEXANOLS

Kurt Flick, Bochum-Stiepel, and Ernst Frankus, Schleckheim, near Aachen, Germany, assignors to Chemie Grunenthal G.m.b.H., Stolberg, Rhineland, Germany
No Drawing. Continuation-in-part of application Ser. No. 357,024, Mar. 30, 1964. This application July 27, 1967, Ser. No. 656,314

Int. Cl. C07d 27/04

U.S. Cl. 260—326.5 M

23 Claims

ABSTRACT OF THE DISCLOSURE

This invention relates to cycloalkanol-substituted phenol ethers having a basic amine group in the cycloalkyl ring, which are useful as analgesic drugs.

The present application is a continuation-in-part of copending application Ser. No. 357,024, filed Mar. 30, 1964 and entitled "Phenol Ethers Containing Basic Groups and a Process of Making Same," and now abandoned.

The present invention relates to new and valuable phenol ethers containing basic groups and, more particularly, to cycloalkanol-substituted phenol ethers having basic groups, to a process of making such compounds, to pharmaceutical compositions containing such compounds, and to a method of using such compounds and compositions therapeutically.

Analgesic drugs are well known. Highly effective analgesic compounds are derived from morphium, such as morphine and other morphine alkaloids. However, it is well known, that morphine as well as other morphium alkaloids produce a number of serious side-effects. More particularly they possess a high degree of tolerance and drug dependence. For this reason numerous attempts have been made to produce analgesic drugs which are substantially free of these side-effects. However, none of these attempts met with complete success.

Foster et al., for instance, disclose in "J. Pharmacol. Exptl. Therap." vol. 91, pages 195 to 209 (1947) (abstracted in "Chemical Abstracts" vol. 42, page 983 (1948); see also: Lee et al. "Jubilee Volume Emil Borell" pages 264 to 309, published Basel 1946, abstracted by Lee in "Medicinal Chemistry" vol. I, page 444, published by John Wiley and Sons, Inc., New York 1951) a number of cyclohexanol derivatives with morphine-like pharmacological activity, in laboratory animals among them, for instance, 1 - (m-methoxy-phenyl) - 2 - piperidino-methyl cyclohexanol-(1) designated by Foster et al. as compound number Nu-640 and its propionic acid ester. These compounds, however, have not only a weak analgesic potency as stated and confirmed by Foster et al. and also in the Lee publications but also a high toxicity so that their therapeutic index is low, rendering the compounds therapeutically useless.

Slomka et al. in "J. Am. Pharm. Assn., Scientific Edition" vol. 40, pages 47 to 51 (1951) disclose compounds of the cyclohexane series which bear a structural relationship to the morphine-type analgesics, among them 1-phenyl-1-acetoxy-2 - dimethylamino methyl cyclohexane hydrochloride and 1 - phenyl - 1-acetoxy-2-diethylamino methyl cyclohexane hydrochloride.

However, these compounds as well as the unesterified 1-phenyl-1-hydroxy - 2 - dialkylamino methyl cyclohexane compounds are analgesically ineffective or, respectively, only slightly effective but of high toxicity.

It is now an object of the present invention to provide valuable therapeutically useful cycloalkanol-sub-

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stituted phenol ethers with a basic group in the cycloalkyl ring and with an alkoxy group in m-position to said cycloalkyl ring, which compounds are substantially free of the disadvantages of the known, above-mentioned compounds of similar structure.

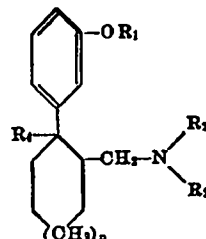
Another object of the present invention is to provide a simple and effective process of making such new and valuable phenol ethers.

A further object of the present invention is to provide pharmaceutical compositions containing, as essential active drug, such phenol ethers.

Still another object of the present invention is to provide a method of relieving pain, of suppressing coughing, and of producing other valuable therapeutic effects by the administration to needful patients of such phenol ethers.

Other objects of the present invention and advantageous features thereof will become apparent as the description proceeds.

In principle, the new and valuable phenol ethers, according to the present invention, have the following Formula I



(I)

wherein:

R₁ indicates alkyl containing 1 to 3 carbon atoms or aralkyl, especially phenyl lower alkyl, such as benzyl or phenyl ethyl;

R₂ and R₃ represent alkyl containing 1 to 6 carbon atoms, aralkyl, especially phenyl lower alkyl, or R₂ and R₃, together with the nitrogen atom to which they are attached, form the morpholine ring or the pyrrolidine ring;

R₄ indicates hydroxyl, halogen, or the lower alkanoyloxy group, especially with 1 to 6 carbon atoms in the alkanoyl moiety; and

n represents the numerals 0, 1 or 2,

and the pharmaceutically acceptable, substantially non-toxic acid addition salts of said phenol ethers.

The compounds of Formula I, especially those in which n stands for the numeral 1 and R₂ and R₃ represent methyl, exhibit strong analgesic activity and are in general well tolerated. For instance the ED₅₀, i.e. the analgesically effective dose, after the administration of which 50% of the test animals do no longer react to pain, of the hydrochloride of 1-(m-methoxy phenyl) - 2 - dimethyl-amino methyl cyclohexanol-(1), when orally administered, is 11.2 mg./kg. of mice body weight. The DL₅₀, i.e. the dose causing death of 50% of the test animals of said compound, when orally administered, is 395.0 mg./kg.

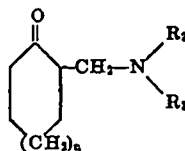
In addition to said analgesic activity, the compounds of Formula I possess excellent antitussive activity. For instance, when intravenously injected, 2.5 mg. of the above-mentioned compound per kg. of cat's body weight inhibit 75% of the mechanically provoked cough reflex. Said cough reflex is also inhibited by intravenous administration of 2.5 mg. of the hydrochloride of 1-(m-methoxy phenyl)-2-pyrrolidino methyl cyclohexanol-(1) per kg. of cat's body weight to 63%, by intravenous administration of 1 mg. of the hydrochloride of 1-(m-benzyloxy phenyl)-2-pyrrolidino methyl cyclohexanol-(1) per kg. of cat's body weight to 65%, and of 2.5 mg. of the hydrochloride of 1-(m-methoxy phenyl)-2-[N-methyl-N-(β-phenyl ethyl)

amino methyl] cyclohexanol-(1) per kg. of cat's body weight to 100%, respectively.

Furthermore, it was found that some of the 2-basically substituted 1-(m-substituted phenyl) cyclohexanol-(1) compounds of Formula I have a noteworthy antiphlogistic and antihistaminic activity. Tests have also shown that the compounds have an analeptic and anticoryza effect and depress the secretion of the nasal mucosa so that they are useful in human therapy, for instance, in the treatment of bronchitis and of the common cold.

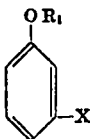
The cycloalkane ring in compounds of Formula I, according to the present invention, contains two carbon atoms, each carrying four different substituents. This configuration causes cis-trans-isomerism. The isomers can be resolved into their optically active forms by methods known per se. The cis- and trans-isomers may be separated from each other, for instance, by fractional distillation of the free bases, by recrystallization of their salts, or by other methods known per se.

The new compounds of Formula I are obtained, for instance, by reacting a basically substituted cycloalkanone compound of Formula II



(II)

wherein R_1 , R_2 and n represent the same substituents and numerals as indicated above, with a phenol ether compound of Formula III



(III)

wherein:

R_1 represents the same substituent as indicated above, while

X represents lithium or the group MgHal wherein Hal represents halogen,

in the presence of an ether, preferably a cyclic ether, and hydrolyzing the intermediate thus obtained to yield the compound of Formula I. Said compound may then be converted into its addition salts with acids and/or into its esters with lower alkanolic acids or hydrogen halides.

To esterify said compounds of Formula I with a lower alkanolic acid, they are preferably reacted with halides or anhydrides of said acids.

Reaction of the compounds of Formula II with the compounds of Formula III is preferably carried out at a temperature between -50°C . and $+100^\circ\text{C}$. Hydrolysis of the intermediates is effected by treating the reaction mixture, preferably while cooling, with water which may contain ammonium salts, or with dilute acids.

The following examples serve to further illustrate the present invention without, however, limiting the same thereto. The melting points and boiling points given have not been corrected.

EXAMPLE 1

Five g. of magnesium turnings are added, while stirring, to a mixture of 37.4 g. of m-bromo anisol and 160 ml. of absolute tetrahydrofuran at such a rate that the reaction mixture boils gently due to the heat produced by the immediately starting reaction. Thereafter, the reaction mixture is refluxed, while being stirred, until the magnesium is completely dissolved. The reaction mixture is cooled to between 0°C . and -10°C . and a mixture of 23.25 g. of 2-dimethylamino methyl cyclohexanone and 45 ml. of absolute tetrahydrofuran is added dropwise thereto. The mixture is stirred at room temperature for about 4 hours and is then poured slowly,

while stirring, into a mixture of 25 g. of ammonium chloride, 50 ml. of water, and 50 g. of ice. The layers formed thereby are separated and the aqueous layer is extracted twice with 50 ml. of ether each. The organic solvent layers are combined, dried over sodium sulfate, and the solvents are evaporated. The residue is distilled, whereby 1 - (m-methoxy phenyl) - 2 - dimethylamino methyl cyclohexanol-(1) is obtained in a yield of 78.6% of the theoretical yield. Boiling point: $138-140^\circ\text{C}/0.6\text{ mm. Hg}$. The hydrochloride obtained from said base, for instance, by dissolving it in ether and treating the solution with dry hydrogen chloride, melts at $168-175^\circ\text{C}$.

The pharmacological test results given hereinabove in column 2 were obtained with said reaction product which is a mixture of the cis- and trans-isomers.

14.7 g. of the above-mentioned hydrochloride are dissolved in 150 ml. of acetic acid anhydride. The solution is heated under reflux for three hours. The solvent is then distilled off in a vacuum. The oily residue is dissolved in acetone. Ether is added thereto until crystallization sets in. The mixture is allowed to stand and the crystals are filtered off. Thereby the hydrochloride of 1 - (m-methoxy phenyl) - 1 - acetoxy - 2 - dimethylamino methyl cyclohexane, melting at $150-155^\circ\text{C}$., is obtained.

By using the same amount of propionic acid anhydride and proceeding in the same manner as described above, the hydrochloride of 1 - (m-methoxy phenyl) - 1 - propionoxy - 2 - dimethylamino methyl cyclohexane of the melting point $198-199^\circ\text{C}$. is obtained.

EXAMPLE 2

Separation of the trans- and cis-isomers

500 g. of the hydrochloride of 1-(m-methoxy phenyl)-dimethylamino methyl cyclohexanol-(1), i.e. of the mixture of the cis- and trans-form as obtained according to Example 1 are heated under reflux with a mixture of 2,500 ml. of anhydrous dioxane and 25 cc. of water for one hour while stirring. The resulting solution is filtered while still hot. The filter residue is again heated under reflux with 1,250 ml. of anhydrous dioxane and filtered while hot. The filter residue obtained thereby is dried until the dioxane is completely removed therefrom. About 300 g. of the hydrochloride of the pure trans-form, i.e. of the racemic 1(e) - (m-methoxy phenyl) - 2(e) - dimethylamino methyl cyclohexane-1(a)-ol, are obtained thereby. Melting point: $180-181^\circ\text{C}$.

The dioxane filtrate yields, on cooling, about 200 g. of white crystals of the melting point $163-165^\circ\text{C}$. These crystals are a mixture of about 20% to 30% of the cis-isomer and about 70% to 80% of the trans-isomer. This mixture cannot be further separated by boiling with dioxane.

The hydrochloride of the pure cis-form, i.e. of the racemic 1(e) - (m-methoxy phenyl) - 2(a) - dimethylamino methyl cyclohexane-1(a)-ol is obtained from said mixture by finely pulverizing said 200 g. in a mortar and stirring it with 2000 ml. of dichloro methane at room temperature for one hour. Thereby, the cis-isomer is not dissolved. After filtering the solution and recrystallizing the filter residue by dissolving it in methanol and adding ether thereto until crystallization sets in, the resulting purified cis-isomer has a melting point of $200-201^\circ\text{C}$.

The dichloro methane filtrate yields, on evaporation, a residue which consists of the substantially pure trans-isomer.

EXAMPLE 3

Resolving the trans-isomer into its optically active forms

50 g. of the hydrochloride of the racemic 1(e) - (m-methoxy phenyl) - 2(e) - dimethylaminomethyl cyclohexane - 1(a) - ol are dissolved in 200 ml. of water. Solid sodium carbonate is added thereto until the solution is

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of strongly alkaline reaction. The alkaline solution is repeatedly extracted with ether, the ether extracts are combined and dried over sodium sulfate. On distilling off the ether, the racemic 1(e) - (m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol is obtained in the form of an oil boiling at 106-110° C./0.01 mm. Hg.

27 g. of said racemic base are dissolved in 100 ml. of acetic acid ethyl ester and the solution is heated under reflux. A solution of 40 g. of dibenzoyl-D-tartaric acid in 200 ml. of acetic acid ethyl ester is added drop by drop thereto. The mixture is heated for two hours. On cooling, 63 g. of the dibenzoyl-D-tartaric acid salt of racemic 1(e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol are obtained.

5 g. of said salt are treated under reflux with 50 ml. of acetic acid ethyl ester for 10 minutes. The hot mixture is filtered. 2.0 g. to 2.2 g. remain as undissolved filter residue. They are recrystallized by dissolving in isopropanol and adding ether thereto until crystallization sets in, and represent the pure dibenzoyl-D-tartaric acid salt of (-) - 1(e) - (m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol of the melting point 132-134° C.; optical rotation $[\alpha]^{25}_D = -76.2^\circ$ (in 96% ethanol).

On cooling the acetic acid ethyl ester solution, 2.4 g. of the dibenzoyl-D-tartaric acid salt of (+)-1(e)-(m-methoxy phenyl) - 2(e) - dimethylamino methyl cyclohexane-1(a)-ol are obtained. They are recrystallized from acetic acid ethyl ester. Melting point: 111-114° C.; optical rotation $[\alpha]^{25}_D = -53^\circ$ (in 96% ethanol).

The hydrochlorides of the optically active bases are obtained from said optically active dibenzoyl-D-tartaric acid salts in the following manner:

2 g. of dibenzoyl-D-tartaric acid salt are dissolved in a mixture of 20 ml. of water and 20 ml. of methanol. An excess of a 20% aqueous sodium hydroxide solution is added thereto. The mixture is repeatedly extracted with ether. The combined ether extracts are dried over sodium sulfate. The ether is then distilled off in a vacuum. The resulting residue is dissolved in acetone and is carefully neutralized by the addition of an ethanol solution of hydrogen chloride while cooling with ice. On addition of ether, the hydrochlorides precipitate in the form of hygroscopic crystals. After drying in a vacuum, the optically active crystals are no more hygroscopic.

The hydrochloride of the (-)-1(e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol has a melting point of 169-170° C.; optical rotation $[\alpha]^{20}_D = -28.0^\circ$ (in water).

The hydrochloride of the (+)-1(e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol has a melting point of 169-170° C.; optical rotation $[\alpha]^{20}_D = +27.5^\circ$ (in water).

When mixing said two optically active hydrochlorides in the proportion 1:1, the resulting mixture corresponds in its melting point and solubility to the racemic starting hydrochloride.

EXAMPLE 4

2.63 g. of the racemic base 1(e)-(m-methoxy phenyl)-2(e)-dimethyl aminomethyl cyclohexane-1(a)-ol obtained according to Example 3, are dissolved in 5 ml. of acetone. 1.16 g. of maleic acid dissolved in 4 ml. of acetone are added thereto. On adding ether to the solution, the maleic acid addition salt of the starting base crystallizes and is filtered off. Its melting point is 68-70° C.

EXAMPLE 5

Following the procedure described in Example 1 but using 2.5 g. of magnesium turnings, 18.7 g. of m-bromo anisol, dissolved in 80 ml. of absolute tetrahydrofuran, and 12.7 g. of 2-dimethylamino methyl cycloheptanone, dissolved in 25 ml. of absolute tetrahydrofuran, 1-(m-methoxy phenyl)-2-dimethylamino methyl cycloheptanol-(1) is obtained in a yield of 73.8% of the theoretical yield.

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Boiling point: 125° C./0.003 mm. Hg. Its hydrochloride melts at 177-181° C.

In the same manner there are obtained, by reacting m-methoxy phenyl magnesium bromide with the appropriate basic ketones, the following compounds:

EXAMPLE 6

1-(m-methoxy phenyl)-2-morpholino methyl cyclohexanol-(1); boiling point: 182-183° C./0.02 mm. Hg; yield: 43.7%; melting point of the hydrochloride: 231-233° C.

EXAMPLE 7

1-(m-methoxy phenyl)-2-pyrrolidino methyl cyclohexanol-(1); boiling point: 145-147° C./0.15 mm. Hg; yield: 55.5%; melting point of the hydrochloride: 174-178° C.

EXAMPLE 8

1 - (m - methoxy phenyl) - 2 - [N - methyl - N - (β-phenyl ethyl) amino methyl]cyclohexanol-(1); boiling point: 167° C./0.006 mm. Hg; yield 56.7%.

EXAMPLE 9

Five g. of magnesium turnings are treated, while stirring, with a solution of 1 ml. of ethyl bromide in 15 ml. of absolute tetrahydrofuran. A solution of 39.5 g. of m-bromo phenol benzylether in 150 ml. of absolute tetrahydrofuran is added to the warm reaction mixture at such a rate that the mixture boils gently. After refluxing for one further hour, the mixture is chilled to 0° C. to -10° C. A solution of 23.3 g. of 2-dimethylamino methyl cyclohexanone in 45 ml. of absolute tetrahydrofuran is added drop by drop thereto, while stirring. The reaction mixture is then stirred at room temperature for four more hours and is slowly poured into a stirred mixture of 25 g. of ammonium chloride, 50 ml. of water, and 50 g. of ice. The layers formed thereby are separated and the aqueous layer is extracted twice with 50 ml. portions of ether. The combined organic solvent layers are dried over sodium sulfate and the solvents are evaporated. On distillation, the residue yields 1-(m-benzyloxy phenyl)-2-dimethylamino methyl cyclohexanol-(1), boiling at 156-160° C./0.003 mm. Hg. Yield: 61% of the theoretical yield. The hydrochloride of this compound melts at 141-143° C.

By treating the hydrochloride with thionylchloride, the hydrochloride of 1 - (m - benzyloxy phenyl) - 1 - chloro-2-dimethylamino methyl cyclohexane is obtained. It melts, after recrystallization from ethanol/ether, at 150-151° C.

By proceeding in the same manner as described in Example 9 there are obtained by reaction of m-benzyloxy phenyl magnesium bromide with the appropriate basic ketones the following compounds:

EXAMPLE 10

1 - (m - benzyloxy phenyl) - 2 - dimethylamino methyl cycloheptanol-(1), boiling point: 167-172° C./0.004 mm. Hg; yield: 45.3%; melting point of the hydrochloride: 140-143° C. Treatment with thionylchloride yields the hydrochloride of 1 - (m - benzyloxy phenyl) - 1-chloro-2-dimethylamino methyl cycloheptane, melting at 124-125° C.

EXAMPLE 11

1 - (m - benzyloxy phenyl) - 2 - pyrrolidino methyl cyclohexanol-(1), boiling point: 175-178° C./0.0002 mm. Hg; yield: 27.4%; melting point of the hydrochloride: 171-173° C.

EXAMPLE 12

1 - (m - benzyloxy phenyl) - 2 - [N - methyl - N - (β-phenyl ethyl) amino methyl] cyclohexanol-(1), boiling point: 220-221° C./0.001 mm. Hg; yield: 46.6%; melting point of the hydrochloride: 173-175° C.

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EXAMPLE 13

1 - (m - benzyloxy phenyl) - 2 - (N - methyl - N-benzylamino methyl) cyclohexanol-(1); boiling point: 208-210° C./0.001 mm. Hg; yield: 40.1%; melting point of the hydrochloride: 188-190° C.

EXAMPLE 14

1 - (m - benzyloxy phenyl) - 2 - morpholino methyl cyclopentanol-(1), boiling point: 200-205° C./0.007 mm. Hg; yield: 43.6%; melting point of the hydrochloride: 169-170° C.

EXAMPLE 15

2.8 g. of small pieces of lithium are added to 150 ml. of absolute ether stored under nitrogen. A few ml. of a solution of 27.5 g. of butyl bromide in 50 ml. of absolute ether are admixed thereto, while stirring. As soon as reaction has set in, the mixture is chilled to -10° C. and the remaining portion of the butyl bromide solution is added dropwise. The reaction mixture is stirred at 0° C. to +10° C. for 2 hours and then chilled to -40° C. to -50° C. While stirring, a solution of 39.5 g. of m-bromo phenol benzyl ether in a mixture of 60 ml. of absolute ether and 90 ml. of absolute tetrahydrofuran, is added slowly. Thereafter, a solution of 23.3 g. of 2-dimethylamino methyl cyclohexanone in 45 ml. of absolute ether is added dropwise thereto. The reaction mixture is stirred at -40° C. for 2 hours. The temperature of the reaction mixture is then allowed to slowly increase to room temperature. The reaction mixture is worked up in the same manner as described in Examples 1 and 9. The same product as in Example 9 is obtained in a yield of 49.1% of the theoretical yield.

EXAMPLE 16

The procedure is the same as described in Example 1. There are used, however, 5 g. of magnesium turnings, 40.2 g. of m-ethoxy bromo benzene dissolved in 160 ml. of absolute tetrahydrofuran, and 23.3 g. of 2-dimethylamino methyl cyclohexanone dissolved in 45 ml. of absolute tetrahydrofuran. 1 - (m - ethoxy phenyl) - 2-dimethylamino methyl cyclohexanol-(1) is obtained thereby. Its boiling point is 134-135° C./0.02 mm. Hg. Melting point of the hydrochloride: 170-175° C.

In place of m-bromo anisol, m-bromo phenol benzyl ether, and m-bromo phenol ethyl ether as used as the one reaction component in the preceding examples, there may be employed equimolecular amounts of other m-halogenated phenol ethers such as m-iodo phenol ethyl

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ether, m-bromo phenol n-propyl ether, m-bromo phenol isopropyl ether, m-iodo phenol β -phenyl ethyl ether and the like m-halogenated alkyl or aralkyl phenol ethers while otherwise the procedure is the same as described in said examples.

In place of 2-dimethylamino methyl, 2-morpholino methyl, 2-pyrrolidinomethyl, 2-[N-methyl-N-(β -phenyl ethyl) amino methyl], 2-(N-methyl-N-benzylamino methyl) cyclopentanones, cyclohexanones, or cycloheptanones used in the preceding examples, there may be employed equimolecular amounts of cyclopentanones, cyclohexanones, or cycloheptanones which are substituted in 2-position by the diethylamino methyl, di-n-propylamino methyl, di-isobutylamino methyl, dipentylamino methyl, dihexylamino methyl, N-methyl-N-ethylamino methyl, dibenzylamino methyl, di- β -phenyl ethylamino methyl, N-butyl-N-benzylamino methyl, and the like basic groups while otherwise the procedure is the same as described in said examples.

The hydroxyl group attached to the cycloalkyl ring in 1-position may be converted into the bromo, iodo, fluoro substituent or into the formyloxy, propionyloxy, butyroyloxy, valeroyloxy, and the like lower alkanoyloxy groups by halogenating or acylating agents according to methods known per se.

As stated hereinabove, the new cycloalkyl-substituted phenol ethers having a basic group attached to the cycloalkyl ring as well as their esters with hydrogen halides or lower alkanic acids can be converted into their acid addition salts. In addition to the hydrochlorides and maleate described hereinabove, other acid addition salts with pharmaceutically acceptable, substantially non-toxic inorganic and organic acids, such as nitric acid, sulfuric acid, phosphoric acid, hydrobromic acid, acetic acid, propionic acid, malonic acid, succinic acid, citric acid, tartaric acid, malic acid, benzoic acid, salicylic acid, phthalic acid, nicotinic acid, and others may also be prepared according to conventional methods of producing such acid addition salts.

Pharmacological tests were carried out with the compounds according to the present invention and with the above-mentioned known compounds of similar structure, especially with the compound designated as Nu-640 by Foster et al. and disclosed by Lee in "Medicinal Chemistry," Lee et al., and Foster et al. as mentioned hereinabove. The following Table I represents the results obtained on testing the compounds for their analgesic and antitussive activity as well as for their toxicity. The therapeutic index, i.e. the quotient LD_{50}/ED_{50} , is given for some of the compounds.

TABLE I

No.	Compound	Analgesic activity ED ₅₀ (mice)	Antitussive activity (cats)	Toxicity LD ₅₀ (mice)	Therapeutic index
1.....	1-(m-methoxyphenyl)-2-piperidino methyl cyclohexanol-(1); Compound Nu 640 of Foster et al.	About 175 mg./kg. on oral administration. Convulsions!	1.0 mg./kg. no effect; 10 mg./kg. slight inhibition; toxic side-effects.	472-551 mg./kg. oral; 333-433 mg./kg. subcutan. 31.2-37.6 mg./kg. i.v.	2.2-2.9.
2.....	1-phenyl-2-dimethylamino methyl cyclohexanol-(1). Unacylated compound (C) (1) of Slomka et al.	With 50 mg./kg. no effect on oral administration.	On i.v. administration of 2.5 mg./kg. no effect.	-----	-----
3.....	Propionic acid ester of No. 2. Next higher homologue of the Slomka et al. compound (C) (1).	With 50 mg./kg. no effect on oral administration.	On i.v. administration of 2.5 mg./kg. no effect.	-----	-----
4.....	Acetic acid ester of 1-phenyl-2-diethylaminomethyl cyclohexanol-(1). Compound (C) (2) of Slomka et al.	50 mg./kg. on oral administration.	Not determined.....	68 mg./kg.....	1.36.
5.....	1-(p-methoxy-phenyl)-2-pyrrolidino methyl cyclohexanol-(1).	100 mg./kg. Convulsions!	No effect.....	-----	-----
6.....	1-(m-methoxyphenyl)-2-dimethylamino methyl cyclohexanol-(1). Compound of Example 1; mixture of cis- and trans-isomers.	11.2 mg./kg. on oral administration.	75% inhibition on i.v. administration of 2.5 mg./kg.	395 mg./kg. on oral administration.	35.2.
7.....	Racemic (e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol. Compound of Example 2; trans-isomer.	9.2 mg./kg. on oral administration. 10.3mg./kg. on subcutan. administration.	-----	510 mg./kg. on oral administration. 68 mg./kg. on i.v. administration.	55.

TABLE I—Continued

No.	Compound	Analgesic activity ED ₅₀ (mice)	Antitussive activity (cats)	Toxicity LD ₅₀ (mice)	Therapeutic index
8.....	Racemic 1(e)-(m-methoxy phenyl)-2(a)-dimethylamino methyl cyclohexane-1(a)-ol. Compound of Example 2; cis-isomer.	Between 50 mg./kg. and 100 mg./kg. on subcutan. administration.	-----	61 mg./kg. on i.v. administration.	Estimated 6-10.
9.....	(+)-1(e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol. Compound of Example 3; D-form of trans-isomer.	9.5 mg./kg. on oral administration. 6.0 mg./kg. on subcut. administration.	-----	425 mg./kg. on oral administration. 45 mg./kg. on i.v. administration.	45.
10.....	(-)-1(e)-(m-methoxy phenyl)-2(e)-dimethyl amino methyl cyclohexane-1(a)-ol. Compound of Example 3; L-form of trans-isomers.	77 mg./kg. on oral administration. 63 mg./kg. on subcut. application.	-----	465 mg./kg. on oral administration. 87 mg./kg. on i.v. administration.	6.
11.....	1-(m-methoxy phenyl)-2-morpholino methyl cyclohexanol-(1) of Example 6.	-----	64% or, resp., 62% cough inhibition on intravenous administration of 1 mg./kg. or, resp., 2.5 mg./kg.	-----	-----
12.....	1-(m-methoxy phenyl)-2-pyrrolidino methylcyclohexanol-(1) of Example 7.	-----	47% or, resp., 61% cough inhibition on intravenous administration of 1 mg./kg. or resp., 2.5 mg./kg.	-----	-----
13.....	1-(m-methoxy phenyl)-2-dimethyl-amino methyl cyclohexanol-(1) of Example 16.	About 30 mg./kg.	-----	-----	-----
14.....	1-(m-methoxy phenyl)-2-dimethylamino methyl cycloheptanol-(1) of Example 5.	50 mg./kg.	-----	-----	-----
15.....	1-(m-benzoyloxy phenyl)-2-dimethylaminomethyl cyclohexanol-(1) of Example 9.	25-50 mg./kg.	-----	-----	-----
16.....	1-(m-benzoyloxyphenyl)-2-dimethylamino methyl cycloheptanol-(1) of Example 10.	-----	50% cough inhibition on intravenous administration of 1 mg./kg.	-----	-----
17.....	1-(m-benzoyloxyphenyl)-2-[N-methyl-N-(β-phenyl ethyl) amino methyl] cyclohexanol-(1) of Example 12.	-----	72% cough inhibition on intravenous administration of 1 mg./kg.	-----	-----
18.....	1-(m-benzoyloxy phenyl)-2-pyrrolidino methyl cyclohexanol-(1) of Example 11.	-----	-----	65% inhibition on i.v. administration of 1 mg./kg.	-----
19.....	1-(m-methoxy phenyl)-2-N-methyl-N-(β-phenyl ethyl) amino methyl cyclohexanol-(1) of Example 8.	-----	-----	50% inhibition on i.v. administration of 1 mg./kg., 100% inhibition on i.v. administration of 2.5 mg./kg.	-----

It is evident that the compounds according to the present invention have a high analgesic activity and a low toxicity so that their therapeutic index is very substantially higher than that of the known compounds described by Lee, Foster et al., and Slomka et al.

In addition thereto most of the compounds according to the present invention have an excellent antitussive activity.

Furthermore, the compounds of this invention and especially 1-(m-methoxy phenyl)-2-dimethylamino methyl cyclohexanol-(1) and its trans-isomer do not affect respiration and blood circulation while the known compound designated as Nu-640 causes depression of respiration and a considerable decrease in blood pressure. The compound according to this invention does not produce any change in the electroencephalogram.

Tests carried out with guinea pigs which are subjected to ultraviolet irradiation until erythema formation show that intramuscular injection of 10 mg./kg. of the trans-isomer of 1-(m-methoxy phenyl)-2-dimethylamino methyl cyclohexanol-(1) causes complete suppression of the erythema up to five hours after irradiation. In contrast thereto the known compound Nu-640 is without effect under these conditions when the same dose is administered. Thus, the compound according to this invention exhibits a pronounced antiphlogistic and anti-inflammatory effect.

Further pharmacological tests with mice and rats indicate that the compounds according to the present invention and especially the trans-isomer of 1-(m-methoxy phenyl)-2-dimethylaminomethyl cyclohexanol-(1) do not cause addiction, i.e. drug dependence, and that they have a low degree of tolerance, i.e. that the doses to produce the same degree of physiological effect need not be increased on repeated administration.

The new compounds are administered orally in the form of powders, tablets, dragées, lozenges, or other solid shaped or liquid preparations. Parenteral and especially intramuscular or intravenous administration in the form of aqueous solutions of their water soluble acid addition

salts or of suspensions of the free bases, and rectal administration in the form of suppositories and the like is also possible.

40 Preparations to be administered orally are obtained for instance, by diluting the active compounds with a solid pulverulent extending agent or pharmaceutical carrier to form an intimate mixture thereof. The components of said mixture are, for instance, intimately mixed in a ball mill or the like device to the desired degree of fineness, or the finely powdered solid carrier is impregnated with a solution of said compound in water or in other suitable solvents, whereafter the water or solvent is removed by evaporation, preferably while milling.

45 50 Tablets, pills, dragées, and the like compressed and shaped preparations are prepared by using the commonly employed diluting agents, binders and the like additives, such as sugar, lactose, talc, starch, bolus alba, pectin; as binders gelatin, gum arabic, methyl cellulose, yeast extract, agar, tragacanth; as lubricants, stearic acid, magnesium stearate, and others.

55 60 The following examples serve to illustrate compositions containing the new cycloalkanol substituted phenol ethers with a basic group in the cycloalkanol ring according to the present invention as they are used in therapy without, however, limiting the same thereto.

EXAMPLE 17

55 70 75 50 g. of the hydrochloride of 1-m-methoxy phenyl-2-dimethylamino methyl cyclohexanol-(1) obtained according to Example 1 and representing the mixture of the trans- and cis-isomers and designated hereinafter as compound A, are intimately mixed with 338 g. of starch, 144 g. of lactose, and 4 g. of o-benzoic acid sulfimide sodium. The mixture is granulated with 140 g. of a 10% aqueous starch paste. The moist granulate is passed through a 1 mm. sieve, dried at 40° C., and again passed through such a sieve. The resulting granulate is mixed with 20 g. of starch, 9 g. of talc, and 1 g. of magnesium stearate. Said mixture is tabletted to tablets of 590 mg., each and a

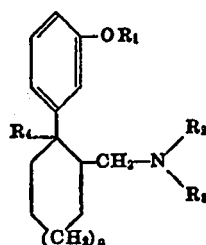
3,652,589

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Of course, many changes and variations in the starting materials and reaction components, in the reaction conditions, temperature, and duration, in the methods used for isolating and purifying the reaction products and for converting them into their esters and acid addition salts, and the like may be made by those skilled in the art in accordance with the principles set forth herein and in the claims annexed hereto.

We claim:

1. The phenol ether compound selected from the group consisting of the cycloalkanol-substituted phenol ether compound having a basic group in its cycloalkyl ring, said compound being of the formula



wherein

R₁ indicates a member selected from the group consisting of alkyl with 1 to 3 carbon atoms and phenyl lower alkyl;

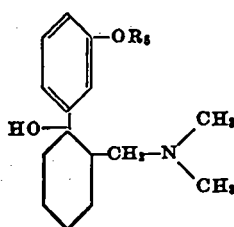
R₂ and R₃ indicate members selected from the group consisting of alkyl with 1 to 6 carbon atoms, phenyl lower alkyl, and R₂ and R₃, together with the nitrogen atom to which they are attached, forming the morpholine ring and the pyrrolidine ring;

R₄ indicates a member selected from the group consisting of hydroxyl, halogen, and the lower alkanoyloxy group; and

n indicates the numerals from 0 to 2;

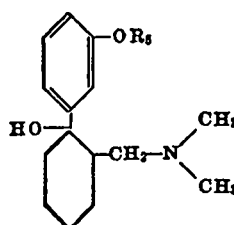
and its pharmaceutically acceptable, substantially non-toxic acid addition salts.

2. The cyclohexanol-substituted phenol ether compound of the formula



wherein R₅ is alkyl with 1 to 3 carbon atoms.

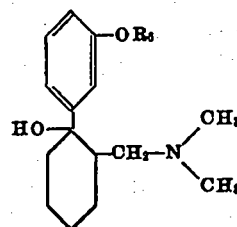
3. The pharmaceutically acceptable, substantially non-toxic acid addition salts of the cyclohexanol-substituted phenol ether compound of the formula



wherein R₅ is alkyl with 1 to 3 carbon atoms.

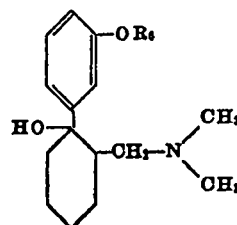
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4. The cyclohexanol-substituted phenol ether compound of the formula



wherein R₆ is phenyl lower alkyl.

5. The pharmaceutically acceptable, substantially non-toxic acid addition salts of the cyclohexanol substituted phenol ether compound of the formula



wherein R₆ is phenyl lower alkyl.

6. 1-(m-methoxy phenyl)-2-dimethylamino methyl cyclohexanol-(1).

7. The hydrochloride of 1-(m-methoxy phenyl)-2-dimethylamino methyl cyclohexanol-(1).

8. 1-(m-methoxy phenyl)-2-pyrrolidino methyl cyclohexanol-(1).

9. The hydrochloride of 1-(m-methoxy phenyl)-2-pyrrolidino methyl cyclohexanol-(1).

10. 1-(m-benzyloxy phenyl)-2-pyrrolidino methyl cyclohexanol-(1).

11. The hydrochloride of 1-(m-benzyloxy phenyl)-2-pyrrolidino methyl cyclohexanol-(1).

12. 1-(m-methoxy phenyl)-2-[N-methyl-N-(β-phenyl ethyl) amino methyl] cyclohexanol-(1).

13. The hydrochloride of 1-(m-methoxy phenyl)-2-[N-methyl-N-(β-phenyl ethyl) amino methyl] cyclohexanol-(1).

14. The racemic 1(e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol.

15. The hydrochloride of the racemic 1(e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol.

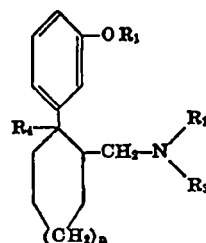
16. The pharmaceutically acceptable, substantially non-toxic acid addition salts of the racemic 1(e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol.

17. (+)-1(e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol.

18. The hydrochloride of the (+)-1(e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol.

19. The pharmaceutically acceptable, substantially non-toxic acid addition salts of the (+)-1(e)-(m-methoxy phenyl)-2(e)-dimethylamino methyl cyclohexane-1(a)-ol.

20. The racemic trans-isomer of the phenol ether compound selected from the group consisting of the cycloalkanol-substituted phenol ether compound having a basic group in its cycloalkyl ring, said compound being of the formula



75 wherein

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(19)



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A61P29:00)**

(54) **Composition comprising a tramadol material and a non-steroidal anti-inflammatory drug**
Zusammensetzung die Tramadol und ein nichtsteroides entzündungshemmenden Mittel enthält
Composition contenant du tramadol et un agent anti-inflammatoire non-stéroïde

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(56) References cited:
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June 1991, Philadelphia, PA, US; abstract no.
122708, MOROZ B. T. ET AL. 'Use of tramadol
hydrochloride in therapeutic operative dentistry
clinical investigation' page 919 ;**

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Description

[0001] United States Patent No. 3,652,589 discloses a class of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1R, 2R or 1S, 2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, commonly known as tramadol, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of tramadol are found in *Arzneim. Forsch. (Drug Res.)*, 28(1), 114(1978). Driessen *et al.*, *Arch. Pharmacol.*, 341, R104 (1990) disclose that tramadol produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the VIth World Congress on Pain, April 1-6 (1990), disclose that tramadol hydrochloride is an orally active pure agonist opioid analgesic. However, clinical experience indicates that tramadol lacks many of the typical side effects of opioid agonists, e.g., respiratory depression (W. Vogel *et al.*, *Arzneim. Forsch. (Drug Res.)*, 28(1), 183 (1978)), constipation (I. Arend *et al.*, *Arzneim. Forsch. (Drug Res.)*, 28(1), 199 (1978)), tolerance (L. Flohe *et al.*, *Arzneim. Forsch. (Drug Res.)*, 28(1), 213 (1978)), and abuse liability (T. Yanagita, *Arzneim. Forsch. (Drug Res.)*, 28(1), 158 (1978)). When given at a dose of 50 mg by rapid i.v. injection, tramadol may produce certain side effects unique to tramadol including hot flushes and sweating. Despite these side effects, tramadol's combination of non-opioid and opioid activity makes tramadol a very unique drug. Tramadol is currently being marketed by Grunenthal GMBH as an analgesic.

[0002] Opioids have for many years been used as analgesics to treat severe pain. They, however, produce undesirable side effects and as a result cannot always be given repeatedly or at high doses. The side effect problems are well documented in the literature. See, for example, J. Jaffe in "Goodman and Gilman's, The Pharmacological Basis of Therapeutics", 8th edition; Gilman *et al.*; Pergamon Press, New York, 1990; Chapter 22; pages 522-573 wherein it is disclosed that morphine and its congeners, e.g., codeine, hydrocodone and oxycodone, are opioid agonist analgesics that exhibit side effects such as respiratory depression, constipation, tolerance and abuse liability.

[0003] As alternatives to using opioids, non-opioids such as acetaminophen, aspirin and ibuprofen are used as analgesics. Ibuprofen, like aspirin, is not subject to the tolerance, addiction and toxicity of the opioid analgesics. However, ibuprofen, aspirin and other nonsteroidal antiinflammatory drugs (commonly referred to as NSAIDs) are only useful in relieving pain of moderate intensity, whereas the opioid analgesics are useful in relieving more intense pain; See Woodbury, D. and Fingl, E. in "The Pharmacological Basis of Therapeutics", 5th Ed.; Goodman, L. and Gilman, A., Chapter 15, (1975).

[0004] To reduce the side effect problems of opioids, opioids have been combined with other drugs including non-opioid analgesic agents, which lower the amount of opioid needed to produce an equivalent degree of analgesia. It has been claimed that some of these combination products also have the advantage of producing a synergistic analgesic effect. For example, A. Takemori, *Annals New York Acad. Sci.*, 281, 262 (1976) discloses that compositions including combinations of opioid analgesics with drugs other than analgesics exhibit a variety of effects, i.e., subadditive (inhibitory), additive or superadditive. R. Taber *et al.*, *J. Pharm. Expt. Thera.*, 169(1), 29 (1969) disclose that the combination of morphine and methadone, another opioid analgesic, exhibits an additive effect. United States Patent No. 4,571,400 discloses that the combination of dihydrocodeine, an opioid analgesic, and ibuprofen, a non-opioid analgesic, provides superadditive effects when the components are within certain ratios. See also U.S. Patent Nos. 4,587,252 and 4,569,937 which disclose other ibuprofen opioid combinations. A. Pircio *et al.*, *Arch. Int. Pharmacodyn.*, 235, 116 (1978) report superadditive analgesia with a 1:125 mixture of butorphanol, another opioid analgesic, and acetaminophen, a non-opioid analgesic, whereas a 1:10 mixture did not show any statistically significant superadditive analgesia.

[0005] Combinations of non-opioid analgesics have also been prepared to avoid the side effects associated with opioids, and the combinations are noted to have the benefit of requiring less of each ingredient and producing superadditive effects. G. Stacher *et al.*, *Int. J. Clin. Pharmacol. Biopharmacy*, 17, 250 (1979) report that the combination of non-opioid analgesics, i.e., tolmetin (another NSAID) and acetaminophen, allows for a marked reduction in the amount of tolmetin required to produce analgesia. In addition, United States Patent No. 4,260,629 discloses that an orally administered composition of acetaminophen and zomepirac, a non-opioid analgesic, in a particular weight ratio range produces a superadditive relief of pain in mammals. Furthermore, United States Patent No. 4,132,788 discloses that 5-aryl-1-(lower)alkylpyrrole-2-acetic acid derivatives, non-opioid analgesics, when combined with acetaminophen or aspirin exhibit superadditive antiarthritic activity. However, there have been warnings against the daily consumption of non-opioid analgesic in large amounts or over long periods (see, D Woodbury and E. Fingl at page 349). In addition, ibuprofen, aspirin and some other NSAIDs may cause gastrointestinal side effects, especially if used repeatedly. See, for example, M.J.S. Langman, *Am. J. Med.* 84 (Suppl. 2A): 15-19, 1988; P.A. Insel in "The Pharmacological Basis of Therapeutics" 8th Ed.; Gilman, A.G. *et al.*, Chapter 26, pp. 664-668, 1990.

[0006] B.T. Moroz *et al.* in *Biological Abstracts* vol. 91, No. 122708 (1991) and *Curr. Ther. Res.* vol 49(3), pages 371-375 (1991) describe the use of tramadol hydrochloride for the treatment of dental pain. Analgesia was found to be most effective when a single dose of tramadol hydrochloride not exceeding 2.5mg/kg was combined with a single oral dose of 400mg of the nonsteroidal anti-inflammatory drug ibuprofen.

[0007] The prior art, however, does not disclose that tramadol, an "atypical" opioid analgesic, can or should be combined with another analgesic to lessen the side effects of each or to yield a composition comprising a tramadol material and another analgesic that exhibits superadditive analgesia.

[0008] It has now been found that a tramadol material which includes various forms of tramadol as defined hereinafter can be combined with nonsteroidal antiinflammatory drugs (hereinafter NSAIDs) to produce analgesia. The combination employs lesser amount of both the tramadol material and the NSAID than would be necessary to produce the same amount of analgesia if either was used alone. By using lesser amounts of both drugs the side effects associated with each are reduced in number and degree. Surprisingly, the compositions comprising the tramadol material and one or more NSAIDs have been found to exhibit synergistic analgesic effects when combined in certain ratios. The present invention provides a pharmaceutical composition comprising a tramadol material and diclofenac. The compositions according to this invention may also be useful in treating tussive conditions.

[0009] In the accompanying drawings:-

[0010] The present invention is generally directed to compositions comprising a tramadol material and diclofenac. The tramadol material is any one of (1R, 2R or 1S, 2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol (tramadol), its N-oxide derivative ("tramadol N-oxide"), and its O-desmethyl derivative ("O-desmethyl tramadol"), or mixtures thereof. It also includes the individual stereoisomers, mixtures of stereoisomers, including the racemates, pharmaceutically acceptable salts of the amines, such as the hydrochloride salt, solvates and polymorphs of the tramadol material. Tramadol is commercially available from Grunenthal or may be made by the process described in United States Patent No. 3,652,589, which is herein incorporated by reference.

[0011] Tramadol N-oxide is prepared by treating tramadol as a free base with an oxidizing agent, e.g., hydrogen peroxide (30%), in an organic solvent, e.g., methanol or isopropanol, with, but preferably without heating. See, "Reagents For Organic Synthesis", 1, 471, Fieser & Fieser eds., Wiley N.Y. (1987), B. Kelentey et al., *Arzneim. Forsch.*, 7, 594 (1957). With heating, the reaction takes about 1 hour, whereas without heating the reaction takes about 3 days. Following the oxidation, the mixture is treated with an agent, e.g., PtO₂ or preferably Pt/C, for about a day, to destroy the excess hydrogen peroxide. The mixture is filtered, followed by the evaporation of the filtrate and then the residue is recrystallized from an organic solvent mixture, e.g., methylene chloride/ethyl acetate.

[0012] O-desmethyl tramadol is prepared by treating tramadol as a free base under O-demethylating reaction conditions, e.g., reacting it with a strong base such as NaH or KH, thiophenol and diethylene glycol (DEG) with heating to reflux. See, Wildes et al., *J. Org. Chem.*, 36, 721 (1971). The reaction takes about an hour, followed by cooling and then quenching in water of the reaction mixture. The quenched mixture is acidified, extracted with an organic solvent such as ethyl ether, basified and then extracted with a halogenated organic solvent such as methylene chloride. The extract is then dried and the solvent evaporated to yield the O-desmethyl product, which may then be short-path distilled, converted to its corresponding salt, e.g., treated with an acidified (HCl/ethanol) solution, and recrystallized from an organic solvent mixture, e.g., ethanol/ethyl ether.

[0013] NSAIDs are non-opioid analgesics characterized in that they are nonsteroidal drugs which act as antiinflammatory, analgesic and anti-pyretic agents. This class of drugs is well known in the art. See for example, Goodman, L. and Gilman, A., *supra*, in Chapter 26 (1990). These drugs share certain therapeutic actions and side effects. Within this broad class of drugs are salicylates, such as aspirin; pyrazolone derivatives such as phenylbutazone, onyphenbutazone, antipyrine, aminopyrine, dipyrrone and apazone; indomethacin; sulindac; fenamates such as mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamic acids; aryl acetic acid and propionic acid compounds such as alphanemethyl-4-(2-thienylcarbonyl) benzene acetic acid (generic name suprofen); 4,5-diphenyl-2-oxazole propionic acid (generic name oxprozin); rac-6-chloro-alphanemethyl-carbazole-2-acetic acid (generic name carprofen); 2-(3-phenyloxyphenyl)-propionic acid, particularly the calcium salt dihydrate thereof (these compounds being referred to generically as fenoprofen and fenoprofen calcium); 2-(6-methoxy-2-naphthyl) propionic acid (generic name naproxen; the generic name of the sodium salt is naproxen sodium); 4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)- α -methylbenzene acetic acid (generic name indoprofen); 2-(3-benzoylphenyl)propionic acid (generic name ketoprofen); and 2-(2-fluoro-4-biphenyl) propionic acid (generic name flurbiprofen) and 1-5-(4-methylbenzoyl)-1H-pyrrole-2-acetic acid (generic name tolmetin). Also included within NSAIDs are compounds within the class including sodium 5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrole-2-acetate dihydrate (generically referred to as zomepirac sodium); 4-hydroxy-2-methyl-N-(2-pyridyl-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (generic name piroxicam); 2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid (generic name diflunisal) or 1-isopropyl-7-methyl-4-phenyl-2(1H)-quinoxalinone (generic name proquazone), phenylacetic acid derivatives such as diclofenac; etodolac and nabumetone.

[0014] The NSAID which is used in the present invention is diclofenac.

[0015] The NSAID and the tramadol material are generally present in a weight ratio of tramadol material to NSAID from 1:1 to 1:200. Certain ratios result in a composition which exhibits synergistic analgesic effects. For example, in a composition comprising a tramadol material and an NSAID, the ratio of the tramadol material: NSAID is preferably from 1:1 to 1:200; and, more preferably, from 1:2 to 1:200. The most preferred ratios are from 1:2 to 1:20. Compositions of a tramadol material and NSAID within these weight ratios have been shown to exhibit synergistic analgesic effects.

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(21) International Application Number: PCT/US92/07542 (22) International Filing Date: 3 September 1992 (03.09.92) (30) Priority data: 755,924 6 September 1991 (06.09.91) US (71) Applicant: McNEILAB, INC. [US/US]; Welsh and McKean Roads, Spring House, PA 19477-0776 (US). (72) Inventor: RAFFA, Robert, B. ; 4 Pacer Lane, Norristown, PA 19401 (US). (74) Agents: CIAMPORCERO, Audley, A. et al.; Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003 (US).		(81) Designated States: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MG, MW, NO, RO, RU, SD, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMPOSITION COMPRISING A TRAMADOL MATERIAL AND ACETAMINOPHEN AND ITS USE (57) Abstract This invention relates to a composition comprising a tramadol material and acetaminophen, and its use. As used herein tramadol refers to various forms of tramadol. The compositions are pharmacologically useful in treating pain and tussive conditions. The compositions are also subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compositions are within certain ratios the pharmacological effects of the compositions are superadditive (Synergistic).		

IV. DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compositions comprising a tramadol material and acetaminophen. The tramadol material is any one of (1R, 2R or 1S, 2S)-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol (tramadol), its N-oxide derivative ("tramadol-N-oxide"), and its O-desmethyl derivative ("O-desmethyl tramadol") or mixtures thereof. It also includes the individual stereoisomers, mixtures of stereoisomers, including the racemates, pharmaceutically acceptable salts of the amines, such as the hydrochloride salt, solvates and polymorphs of the tramadol material. Tramadol is commercially available from Grunenthal or may be made by the process described in United States Patent No. 3,652,589, which is herein incorporated by reference.

Tramadol-N-oxide is prepared by treating tramadol as a free base with an oxidizing agent, e.g., hydrogen peroxide (30%), in an organic solvent, e.g., methanol or isopropanol, with and preferably, without heating. See, "Reagents For Organic Synthesis", 1, 471, Fieser & Fieser eds., Wiley N.Y; (1987), B. Kelentey et al., Arzneim. Forsch., 7, 594 (1957). With heating, the reaction takes about 1 hour, whereas without heating the reaction takes about 3 days. Following the oxidation, the mixture is treated with an agent, e.g. PtO₂ or preferably Pt/C, for about a day, to destroy the excess hydrogen peroxide. The mixture is filtered, followed by the evaporation of the filtrate and then the residue is recrystallized from an organic solvent mixture, e.g., methylene chloride/ethyl acetate.

O-Desmethyl tramadol is prepared by treating tramadol as a free base under O-desmethylating reaction conditions, e.g., reacting it with a strong base such as NaH or KH thiophenol and diethylene glycol (DEG) with heating to reflux. See, Wildes et al., J. Org. Chem., 36, 721 (1971). The reaction takes about an hour, followed by the cooling and then quenching in water of the reaction mixture. The quenched mixture is acidified, extracted with an organic solvent such as ethyl ether, basified and then extracted with a halogenated organic solvent such as methylene chloride. The extract is then dried and the solvent evaporated to yield the O-desmethyl product, which may then be short-path distilled, converted to its corresponding salt, e.g., treated with an acidified (HCl ethanol) solution, and recrystallized from an organic solvent mixture, e.g., ethanol/ethyl ether.

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54 Tramadolsalz enthaltende Arzneimittel mit verzögerter Wirkstofffreisetzung.

57 Es werden Arzneimittel in Tablettenform zur oralen Applikation beschrieben, aus denen ein feuchtigkeitsunempfindliches, physiologisch verträgliches Tramadolsalz verzögert freigesetzt wird und die wenigstens einen pharmazeutisch akzeptablen Matrixbildner enthalten.

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Die Erfindung betrifft Arzneimittel in Tablettenform zur oralen Applikation, aus denen ein feuchtigkeitsunempfindliches, physiologisch verträgliches Salz von Tramadol verzögert freigesetzt wird und die mindestens einen pharmazeutisch akzeptablen Matrixbildner enthalten.

Tramadolhydrochlorid - (1RS;2 RS)-2[(Dimethylamino)methyl] -1-(3-methoxyphenyl)cyclohexanol, Hydrochlorid - ist ein Analgetikum, das bei starken und mittelstarken Schmerzen wirksam ist. Alle zur Zeit im Markt befindlichen Arzneiformen setzen Tramadolhydrochlorid unverzögert frei, so daß diese Arzneimittel zur Erzielung einer guten therapeutischen Wirksamkeit bei anhaltenden Schmerzen 3- bis 4mal täglich vom Patienten eingenommen werden müssen. Für die Patienten würde es daher eine Erleichterung bedeuten, wenn die Verabreichungsfrequenz auf 1- bis 2mal täglich reduziert werden könnte.

Verschiedene prinzipielle Ausführungsformen von Retardzubereitungen sind dem Fachmann bekannt. So wird beispielsweise in dem bereits am 19. April 1960 angemeldeten Schutzrecht US 3,065,143 eine Retardtablette offenbart, die einen pharmazeutisch akzeptablen hydrophilen Gummi enthält, der schnell Wasser absorbiert und bei 37° C quillt und dessen Gewichtsanteil in der Tablette wenigstens ein Drittel beträgt. Wenn die Tablette in Kontakt mit dem wäßrigen Medium des Gastrointestinaltraktes gebracht wird, bildet sich eine weiche Gelbarriere auf der Tablettenoberfläche, die einen schnellen Zerfall der Tablette und eine schnelle Wirkstofffreigabe verhindert und einen langsamen Zerfall mit der Freigabe des Wirkstoffes über einen Zeitraum von mindestens 4 Stunden ermöglicht. Die Beispiele zeigen jedoch, daß die Wirkstofffreisetzung aus den Tabletten vom pH-Wert beeinflusst wird. Weiterhin wird beschrieben, daß zur Freisetzung eines Wirkstoffes die äußere Gelschicht durch die Bewegungen im Gastrointestinaltrakt abgeschert wird, wodurch der Wirkstoff aus dem Gel freigesetzt wird. Gleichzeitig bildet sich an der dann freien Tablettenoberfläche eine neue Gelschicht. Die Wirkstofffreisetzung wird daher auch durch mechanische Beanspruchung beeinflusst. Desweiteren wird beschrieben, daß die Freisetzungsgeschwindigkeit vom Gewichtsverhältnis Wirkstoff zu Gummi sowie vom Gehalt an hydrophilem Gummi in der Tablette abhängig ist.

In US 4,389,393 (Reexamination Certificate B 1 4,389,393) wird ein Trägermaterial für feuchtigkeitsempfindliche Wirkstoffe offenbart, das, zu einer festen Dosierungseinheit geformt und gepreßt, eine regelmäßige und verzögerte Wirkstofffreisetzung nach der Verabreichung zeigt. Das Trägermaterial besteht aus einer oder mehreren Hydroxypropylmethylcellulosen oder aus einer Mischung aus einer oder mehreren Hydroxypropylmethylcellulosen und bis zu 30 Gew.-% aus Methylcellulose, Natriumcarboxymethylcellulose und/oder einem anderen Celluloseether, wobei wenigstens eine der Hydroxymethylpropylcellulosen einen Methoxygehalt zwischen 16 und 24 Gew.-%, einen Hydroxypropoxygehalt zwischen 4 und 32 Gew.-% und ein numerisches mittleres Molekulargewicht von mindestens 50.000 aufweist. Das Trägermaterial ist zu 30 Gew.-% oder weniger in der Dosierungsform enthalten und bewirkt, daß wenigstens 4 Stunden für die Freisetzung von 94,4 % des feuchtigkeitsempfindlichen Wirkstoffes aus der Dosierungsform nach der Verabreichung erforderlich sind.

In Int. J. Pharm. Tech. & Prod. Mfr. 5, 1 (1984) werden hydrophile Matrices, insbesondere Hydroxypropylmethylcellulosen, für orale Dosierungsformen mit kontrollierter Wirkstofffreisetzung beschrieben. Auf den Seiten 4 bis 6 dieses Dokumentes wird ausgeführt, daß die Freisetzungsgeschwindigkeit eines Arzneistoffes sowohl von der Viskosität als auch vom Gewichtsanteil des eingesetzten Polymers abhängt. Desweiteren beeinflussen Größe und Form der Dosierungseinheit die Freisetzung, wohingegen praktisch keine Abhängigkeit vom Herstellungsprozeß durch Granulation oder Direkttablettierung besteht. Dagegen zeigen unterschiedliche Füllstoffe in der Rezeptur einen starken Einfluß auf die Wirkstofffreisetzung. Gemäß den Abbildungen 16 und 18 bewirken unlösliche Hilfsstoffe eine Beschleunigung der Freisetzung bis hin zur vollständigen Aufhebung des Effektes der kontrollierten Freisetzung, unabhängig davon, ob diese Stoffe, wie zum Beispiel mikrokristalline Cellulose, quellen können oder diese Stoffe wie zum Beispiel Calciumhydrogenphosphat, nicht quellbar sind.

Aus Int. J. Pharm. 40, 223 (1987) ist bekannt, daß die Freisetzungsgeschwindigkeit eines Wirkstoffes aus einer Retardtablette, deren Matrixbildner Hydroxypropylmethylcellulose ist, vom Gewichtsverhältnis Wirkstoff zu Hydroxymethylpropylcellulose abhängt. Je mehr dieses Verhältnis zu Gunsten des Wirkstoffes verschoben ist, desto höher ist die Freisetzungsgeschwindigkeit. In Zubereitungen, die mehr als 50 Gew.-% Füllstoff enthalten, wird die Freisetzungsgeschwindigkeit durch die Art der verwendeten Hilfsstoffe beeinflusst. Ein teilweiser Ersatz von Hydroxypropylmethylcellulose durch einen Füllstoff und damit verbunden eine Verringerung des Gehaltes an Hydroxypropylmethylcellulose in der Zubereitung führt zu einer Erhöhung der Freisetzungsgeschwindigkeit.

Die in J. Pharm. Sci. 57, 1292 (1968) beschriebenen Matrix-Retardtabletten führen bei einer Erhöhung der löslichen Anteile in der hydrophilen Matrix zu einer Erhöhung der Freisetzungsgeschwindigkeit.

Die der Erfindung zugrundeliegende Aufgabe bestand darin, Arzneimittel in Tablettenform zur oralen Applikation bereitzustellen, aus denen ein feuchtigkeitsunempfindliches, physiologisch verträgliches Salz von Tramadol, unabhängig vom pH-Wert der Freisetzungsumgebung und unabhängig von der Art und

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(21) International Application Number: PCT/US96/18904 (22) International Filing Date: 14 November 1996 (14.11.96) (30) Priority Data: 08/557,279 14 November 1995 (14.11.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/557,279 (CIP) Filed on 14 November 1995 (14.11.95) (71) Applicant (for all designated States except US): EURO- CELTIQUE, S.A. [LU/LU]; 122, boulevard de la Petrusse, L-2330 Luxembourg (LU). (72) Inventors; and (75) Inventors/Applicants (for US only): ALFONSO, Mark [US/US]; 104 Wedgewood Drive, Easton, CT 06612 (US). GOLDENHEIM, Paul [US/US]; 4 Bald Hill Place, Wilton, CT 06897 (US). SACKLER, Richard [US/US]; 25 Windrose Way, Greenwich, CT 06830 (US).			(74) Agents: DAVIDSON, Clifford, M. et al.; Steinberg, Raskin & Davidson, P.C., 1140 Avenue of the Americas, New York, NY 10036 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, 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). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: FORMULATION FOR RESPIRATORY TRACT ADMINISTRATION			
(57) Abstract A dosage form for intranasal and/or inhalation administration of an analgesic having low opioid receptor binding activity to a warm blooded animal, that includes a pharmaceutically effective amount of the analgesic. A preferred analgesic is tramadol, a tramadol and/or a pharmaceutically acceptable salt, metabolite or derivative thereof. Methods of making and using the formulation according to the invention are also provided.			

FORMULATION FOR RESPIRATORY TRACT ADMINISTRATION

FIELD OF THE INVENTION

5 The present invention relates to formulations and methods for the intranasal and inhalation administration of analgesics having low opioid receptor binding affinity.

BACKGROUND OF THE INVENTION

10 Pharmacologically active compounds are most commonly administered by the oral route. In particular, analgesics are preferably taken by mouth. However, this convenient route of administration is not always possible for certain patients. Contraindications to oral administration of analgesics can include nausea and/or emesis, oral or gastrointestinal surgery and dysphagia. In addition, rate of analgesia onset is slower and more variable due to first pass effects which compromise the apparent potency of some analgesics and complicate
15 their use. The alternative of administration by injection, e.g., parenteral, intramuscular or subcutaneous injection, is generally not preferred due to patient discomfort and the attendant increased costs associated with the production of and administration of injectable products.

 Another, less invasive form of administration is transmucosal administration. Transmucosal administration can be via oral, nasal and/or upper respiratory tract, rectal or
20 vaginal mucosal surfaces, to name the more common non-oral transmucosal routes of administration. Transmucosal administration has the advantage that patients who are unable to swallow can be medicated without recourse to injection. Importantly, transmucosal administration may often provide a more rapid relief of pain, compared to oral administration, by providing direct access to the blood circulation and bypassing the gastrointestinal tract and portal vein circulation and liver metabolism. A particularly preferred route enterohepatic blood circulation. A particularly preferred route for transmucosal delivery is intranasal administration for absorption by the nasal mucosal surfaces and/or inhalation for absorption in the bronchial passages of the lungs.

 Heretofore, it has been taught that only certain opioid analgesic compounds would be suitable for intranasal transmucosal administration. For example, given the difficulties of delivering compounds across the mucosal barrier and the limited mucosal area that is

conventional strong opioid receptor binding agents. Therefore, the art does not disclose that a weak opioid receptor binding compound, such as the analgesic tramadol, or its derivatives and pharmaceutically acceptable salts, can be delivered by transmucosal and/or inhalation administration.

5 Tramadol, which has the chemical name ($\pm$) trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops, suppositories and formulations for systemic injection, containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain
10 (e.g., ZYDOL, by Searle; more recently ULTRAM, by Ortho-McNeil Pharmaceutical). Tramadol hydrochloride is currently administered in single oral doses of 50, 75, 100, 150 and 200 mg to patients with, e.g., postoperative pain. In addition, controlled release preparations for oral administration of tramadol are disclosed by co-owned application, U.S. Serial number 08/241,129, filed on May 10, 1994, the disclosure of which is incorporated herein by
15 reference.

Tramadol is a centrally acting synthetic analgesic compound. Unlike conventional opioids, the mechanism of action of tramadol is not completely understood. However, it is known that tramadol binds opioid receptors at low affinity and that the tramadol metabolite
20 mono-O-desmethyltramadol (denoted "M1") binds to opioid receptors at high affinity. The M1 metabolite exhibits substantially greater analgesic activity in animal models than does tramadol. It is also known that tramadol antagonizes reuptake of both norepinephrine and serotonin (in vitro), which may also contribute to the analgesic action of tramadol. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times
25 more potent in opioid receptor binding. However, the contribution to human analgesia of tramadol relative to tramadol metabolite M1 is unknown. The unconventional nature of tramadol-induced antinociception is confirmed by reports that the opioid antagonist naloxone only partially antagonizes tramadol-induced antinociception in animal models. Thus, tramadol exhibits both a unique chemical structure and mechanism of action relative to
30 conventional opioids.

Heretofore there has been no acceptable method or formulation for the transmucosal administration of tramadol, an analgesic which is believed to provide analgesic activity by

either or both opioid and non-opioid mechanisms, which is readily absorbed by the oral route and which is not of the highest opioid receptor binding.

OBJECTS OF THE INVENTION

5 It is accordingly an object of the present invention to provide a pharmaceutical dosage form of an opioid that binds weakly to opioid receptors that can be administered intranasally and/or by inhalation.

Another object of the present invention is to provide a pharmaceutically acceptable dosage form of tramadol that can be administered intranasally and/or by inhalation.

10 Still another object of the present invention is to provide a method of treating a patient with a pharmaceutically acceptable dosage form dosage form of tramadol or its derivatives or pharmaceutically acceptable salts via intranasal and/or inhalation administration.

SUMMARY OF THE INVENTION

15 In accordance with the above objects and others which will be apparent from the further reading of the specification and of the appended claims, the present invention is related to the surprising discovery that an analgesic that is a weak opioid receptor binding compound can be effectively administered to a warm blooded animal, including a human patient, by administering a pharmaceutically effective amount of the compound, or a
20 pharmaceutically acceptable salt, to the respiratory tract mucosal surfaces of an animal in need of treatment.

The invention also provides for a dosage form for intranasal and/or inhalation administration of a weak opioid or non-opioid analgesic, to a warm blooded animal.

The invention also provides for a method for producing analgesia in a warm blooded
25 animal, such as a human patient, comprising contacting respiratory tract mucosal surfaces, such as the nasal and/or bronchial mucosal surfaces of a warm blooded animal in need of analgesia, with an analgesically effective amount of a weak opioid or non-opioid analgesic.

The compound can be, for example, the weak opioid analgesic tramadol, either as the free base, and/or as its pharmaceutically acceptable derivatives, salts and active metabolites
30 or in any combination thereof. The compound can be administered to the respiratory tract either intranasally and/or by inhalation.

The dosage form can include a pharmaceutically effective amount of a weak opioid or non-opioid analgesic, such as, e.g., tramadol as described above, together with a pharmaceutically acceptable carrier that is suitable for intranasal and/or inhalation administration. The dosage form can contain, for example, tramadol HCl in an amount ranging from 5 mg to 500 mg per spray, puff or inhalation.

The dosage form suitable for intranasal and/or inhalation administration can be in the form of, e.g., a liquid solution, suspension, emulsion, liposome, paste or similar such multiphasic composition or other art-known pharmaceutical dispersion. Preferably, the dosage form includes a carrier of isotonic saline and a pharmaceutically acceptable buffer.

For intranasal administration alone, the dosage form may also include an emulsion, a paste, a cream and/or a gel or gauze packing impregnated with the analgesic to be administered. A useful tramadol metabolite, that is also analgesically active, is for example, mono-O-desmethyltramadol, which can also be so administered at an effective dose intranasally and/or by inhalation alone or in combination with another drug, such as, for example, a tramadol and/or a salt or derivative thereof.

DETAILED DESCRIPTION

Accordingly, the present invention provides compositions and methods having utility for the administration, via the respiratory tract, of analgesic drugs having low opioid receptor binding activity. Preferably, the analgesic drugs include the analgesic drug tramadol and derivatives and salts thereof. Reference to "tramadol" herein, unless indicated otherwise, is also understood to encompass all pharmaceutically acceptable forms of tramadol, either as the free base and/or as its pharmaceutically acceptable derivatives, salts and active metabolite and/or combinations thereof, all of which are contemplated to be used in the present compositions and methods. Reference to the term "salt" herein, i.e., tramadol salt, is also intended to encompass the haloacids, i.e., tramadol HCl and the like, unless otherwise indicated.

In accordance with the present invention, an effective amount of a pharmaceutically acceptable form of tramadol is administered intranasally, e.g., by contact with mucosal surfaces in the nasal passages.

Pharmaceutically acceptable carriers for administering tramadol to the nasal mucosal

surfaces will be readily appreciated by the ordinary artisan. Such carriers are disclosed, simply by way of example, by Remington's Pharmaceutical Sciences" 16th edition, 1980, Ed. By Arthur Osol, the disclosure of which is incorporated by reference herein in its entirety.

The selection of appropriate carriers depends upon the particular type of administration that is contemplated. For administration via the upper respiratory tract, e.g., the nasal mucosal surfaces, tramadol can be formulated into a solution, e.g., water or isotonic saline, buffered or unbuffered, or as a suspension, for intranasal administration as drops or as a spray. Preferably, such solutions or suspensions are isotonic relative to nasal secretions and of about the same pH, ranging e.g., from about pH 4.0 to about pH 9.00, from about pH 4.0 to about pH 7.4 or, from pH 6.0 to pH 7.0. Buffers should be physiologically compatible and include, simply by way of example, phosphate buffers. For example, a representative nasal decongestant is described as being buffered to a pH of about 6.2 (Remington's, Id. at page 1445). Of course, the ordinary artisan can readily determine a suitable saline content and pH for an innocuous aqueous carrier for nasal and/or upper respiratory administration.

Tramadol containing intranasal carriers include nasal gels, creams, pastes or ointments with a viscosity of, e.g., from about 10 to about 3000 cps, or from about 2500 to 6500 cps, or greater, may also be used to provide a more sustained contact with the nasal mucosal surfaces. Such carrier viscous formulations may be based upon, simply by way of example, alkylcelluloses and/or other biocompatible carriers of high viscosity well known to the art (see e.g., Remington's, cited *supra*. A preferred alkylcellulose is, e.g., methylcellulose in a concentration ranging from about 5 to about 1000 or more mg per 100 ml of carrier. A more preferred concentration of methyl cellulose is, simply by way of example, from about 25 to about mg per 100 ml of carrier. The carrier containing the drug can be soaked into a fabric material, such as gauze, that can be applied to the nasal mucosal surfaces to allow for drug penetration therein.

Other ingredients, such as art known preservatives, colorants, lubricating or viscous mineral or vegetable oils, perfumes, natural or synthetic plant extracts such as aromatic oils, and humectants and viscosity enhancers such as, e.g., glycerol, can also be included to provide additional viscosity, moisture retention and a pleasant texture and odor for the formulation. For nasal administration of solutions or suspensions according to the invention, various devices are available in the art for the generation of drops, droplets and sprays. For

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(54) Process for the purification of (RR-SS)-2-dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexanol hydrochloride ✓

(57) The invention provides a process for the separation of (RR,SS) 2-dimethylaminomethyl-1-(3-methoxyphenyl) cyclohexanol hydrochloride [(RR,SS)-Tramadol], from a mixture consisting of (RR,SS) Tramadol and (RS,SR)-2-dimethylaminomethyl-1-(3-methoxyphenyl)

cyclohexanol [(RS,SR)-Tramadol], which process includes combining the mixture with an electrophilic reagent, the reagent selectively reacting with the hydroxyl group of (RS,SR)-Tramadol, leaving most of the (RR,SS) Tramadol intact, and precipitating the remaining, practically pure (RR,SS) Tramadol from the mixture.

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Description

Field of the Invention

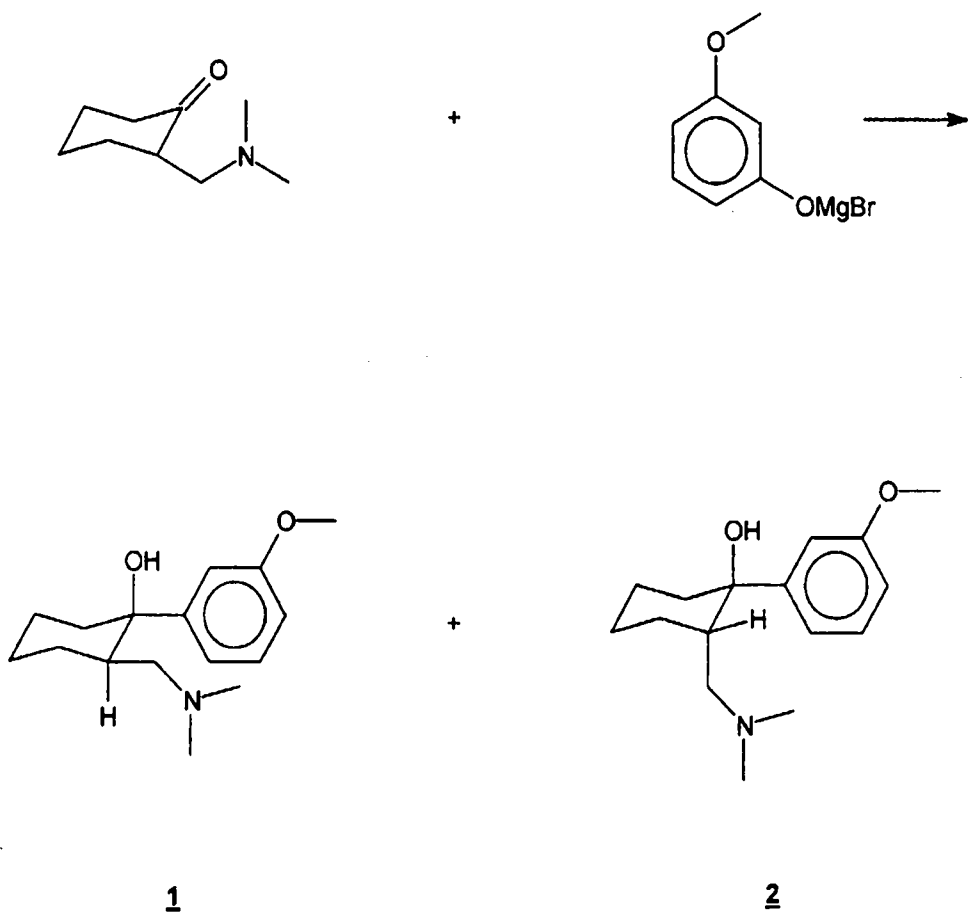
The present invention relates to a process for the purification of (RR,SS)-2-dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexanol hydrochloride, also known as trans Tramadol, from its (RS,SR) isomer and from other undesirable products.

More particularly, the present invention relates to a process for the purification of the (RR,SS) isomer, based on the discovery that the hydroxyl group of the (RS,SR) isomer undergoes various chemical reactions faster than the same group of the (RR,SS) isomer. Thus, the invention is based on reacting a mixture of isomers with various chemical substances reacting predominantly with the (RS,SR) isomer, while the (RR,SS) isomer remains practically intact. The desired (RR,SS) isomer is then easily purified by recrystallization from an appropriate solvent.

Background of the Invention

Tramadol is a well established pain killer, invented by Gruenenthal GmbH, Germany, used as a non-addictive analgesic and sold under different trade names such as Tramal, Ultram, Crispin and Tramundin.

The synthesis of Tramadol is described in U.S. Patent No. 3,652,589 and in British Patent No. 992,399. The synthesis of Tramadol consists of a Grignard reaction between 2-dimethylaminomethylcyclohexanone and 3-methoxyphenyl magnesium bromide (Equation 1). From the reaction scheme, it is clear that both isomers (RR,SS) (Structure 1) and (RS, SR) (Structure 2) are obtained in variable ratios, depending on the reaction conditions.



EQUATION 1

The original patents assigned to Gruenenthal GmbH describe the isolation of the (RR,SS) isomer, as follows:

The complex mixture of products containing both isomers of Tramadol obtained from the Grignard reaction is distilled under reduced pressure. The isomers are distilled together at 138-140°C (0.6 mm Hg). The distillate is dissolved in ether and is reacted with gaseous HCl. The resulting mixture of both isomers of Tramadol is precipitated as hydrochlorides and filtered. The resulting mixture contains about 20% of the (RS,SR) isomer. The isomer mixture is then refluxed twice with five volumes of moist dioxane, and filtered. The cake obtained consists of pure (RR,SS) isomer. The residual solution consists of "a mixture of about 20-30% of the cis (i.e. RS,SR), which cannot be further separated by boiling dioxane" [U.S. Patent 3,652,589, Example 2].

Dioxane, used in large quantities in this process, possesses many undesirable properties. It has recently been listed as a Category I carcinogen by OSHA [Kirk & Othmer, 3rd Ed., Vol. 9, p. 386], and it is known to cause CNS depression and liver necrosis [ibid., Vol. 13, p. 267]; in addition, it tends to form hazardous peroxides [ibid., Vol 17, p. 48]. As a result, the concentration of dioxane in the final product has been strictly limited to several ppb's, and the DAC (1991) restricted the level of dioxane in Tramadol to 0.5 ppm.

A different separation method, described in Israeli Specification No. 103096, takes advantage of the fact that the precipitation of the (RR,SS) isomer of Tramadol from its solution in medium chained alcohols (C₄-C₈) occurs faster than the precipitation of the (RS,SR) isomer, which tends to separate later. The main disadvantage of this method is, that the time interval between the end of separation of the (RR,SS) isomer and the beginning of the (RS,SR) isomer separation is variable, and seems to depend sharply on the composition of the crude mixture. Therefore, variations in the yield and the quality of the product often occur. Furthermore, about 40% of the (RR,SS) isomer does not separate and remains in solution, along with the (RS,SR) isomer. This remaining mixture cannot be further purified by this method.

Another method, described in Israeli Specification No. 116281, relies on the fact that the (RS,SR) isomer of Tramadol undergoes dehydration much faster than the (RR,SS) isomer, when treated with 4-toluenesulfonic acid, or sulfuric acid; furthermore, when the reaction is carried out in an aqueous medium, a certain amount (up to 50%) of the (RS,SR) isomer is converted to the (RR,SS) isomer. This may, of course increase the efficiency of the process.

The unreacted (RR, SS) isomer is then separated from the dehydrated products and from other impurities by simple crystallization.

While further examining the results of the latter process, it was surprisingly found that the hydroxyl group of the (RS,SR) isomer of Tramadol reacts faster than the same group of the (RR,SS) with various reagents. A plausible explanation for this observation can be supplied by comparing the structures of both isomers, and their ability to form hydrogen bonds.

Looking closely at Fig. 1 [(RR,SS) Tramadol hydrochloride] and at Fig. 2 [(RS,SR) Tramadol hydrochloride], one can provide a plausible explanation for the difference in the OH group's activity, as follows: The proton attached to the nitrogen atom of the protonated (RR,SS) isomer of Tramadol is capable of forming a stable hydrogen bonding with the oxygen atom of the hydroxyl group (see Fig. 1). Thus, any reaction involving protonation of the hydroxyl group (such as dehydration), or any reaction in which the hydroxyl group reacts as a nucleophile (such as a nucleophilic substitution or esterification process) is less favored to occur.

In the (RS,SR) isomer, on the other hand, there is no possible way of forming a stable intramolecular hydrogen bond, and therefore, any of the above-mentioned types of reactions can easily occur, considering the fact that this particular hydroxyl group is tertiary and benzylic.

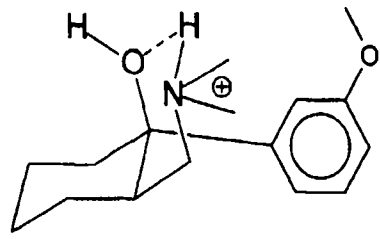


figure 1

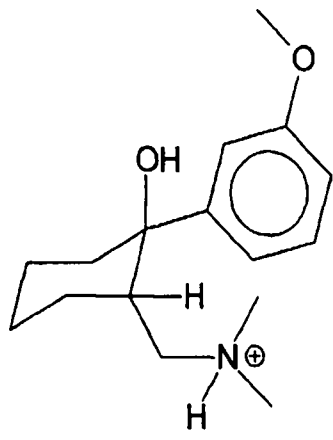


figure 2

The general purification procedure of the present invention consists of reacting a mixture of both geometrical isomers of Tramadol hydrochloride with a potential electrophile under such conditions that the (RS,SR) isomer reacts almost exclusively, while the (RR,SS) isomer remains practically intact. The resulting mixture is evaporated and the resulting solid substance is then recrystallized from isopropanol or any other suitable solvent.

Summary of the Invention

Thus, according to the present invention, there is now provided a process for the separation of (RR,SS)-2-dimethylaminomethyl-1-(3-methoxyphenyl) cyclohexanol hydrochloride [(RR,SS)-Tramadol], from a mixture consisting of (RR,SS)-Tramadol and (RS,SR)-2-dimethylaminomethyl-1-(3-methoxyphenyl) cyclohexanol [(RS,SR)-Tramadol], comprising combining said mixture with an electrophilic reagent, said reagent selectively reacting with the hydroxyl group of (RS,SR)-Tramadol, leaving most of the (RR,SS)-Tramadol intact, and precipitating the remaining, practically pure (RR,SS)-Tramadol from said mixture.

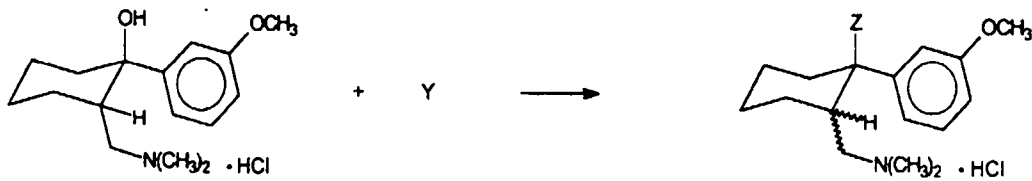
In a first preferred embodiment of the present invention, said electrophilic reagent is an acetylating agent, preferably acetic anhydride.

In a second preferred embodiment of the present invention, said electrophilic reagent is a halogen-providing substitution agent, preferably chlorine. An especially preferred agent is thionyl chloride.

In another preferred embodiment of the present invention, there is provided a process for the separation of a mixture consisting of (RR,SS)-2-dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexanol hydrochloride and (RS,SR)-2-dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexanol hydrochloride, comprising selectively reacting said (RS,SR) isomer with a salt of hydrazoic acid in acidic medium; neutralizing the resulting solution; precipitating the remaining practically pure (RR,SS) Tramadol with hydrogen chloride from an alcoholic solution; and purifying the precipitated (RR,SS) isomer by recrystallization.

In another preferred embodiment of the invention, said reaction is carried out with sodium azide in the presence of trifluoroacetic acid.

More particularly, the above-mentioned isomer mixture is reacted with acetic anhydride, thionyl chloride or hydrazoic acid; 1-acetoxy-1-(3-methoxyphenyl)-2-dimethylaminomethyl cyclohexane, 1-chloro-1-(3-methoxyphenyl)-2-dimethylaminomethyl cyclohexane, and 1-azido-1-(3-methoxyphenyl)-2-dimethylaminomethyl cyclohexane (as the hydrochloride salts) are respectively formed, mainly originating from the more reactive (RS,SR) isomer, as shown in Equation 2:



- | | | | |
|----|-----------------------|----|--------------------|
| A. | Y = Ac ₂ O | A. | Z = OAc |
| B. | Y = SOCl ₂ | B. | Z = Cl |
| C. | Y = HN ₃ | C. | Z = N ₃ |

EQUATION 2

While the invention will now be described in connection with certain preferred embodiments in the following examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily

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understood description of formulation procedures as well as of the principles and conceptual aspects of the invention.

Example 1

11.1 g of a mixture consisting of 77% (RR,SS) Tramadol hydrochloride and 23% of the corresponding (RS,SR) isomer were dissolved in 30 ml DMF. 1.3 g acetic anhydride were added and the reaction mixture was stirred at room temperature for 12 hours. The solvent was partly evaporated under reduced pressure and 15 ml toluene were added. The suspension obtained was filtered and washed with 5 ml toluene. 5.8 g of crystals were obtained, in which the (RR,SS):(RS,SR) isomer ratio was 70:1. The product obtained was crystallized from 12 ml isopropanol and 4 g of pure (RR,SS) Tramadol hydrochloride were obtained.

Example 2

19.5 g of a mixture consisting of 60.5% (RR,SS) Tramadol hydrochloride and 40.5% of the corresponding (RS,SR) isomer were suspended in 55 ml chlorobenzene. A solution of 4 ml thionyl chloride in 15 ml chlorobenzene was added dropwise for two hours. The suspension was partly evaporated, the residue was filtered and rinsed with toluene, and 8.1 g of crystals were obtained, in which the (RR,SS):(RS,SR) isomer ratio was 14:1. The product obtained was recrystallized from isopropanol, and 6.7 g of pure (RR,SS) Tramadol hydrochloride were obtained.

Example 3

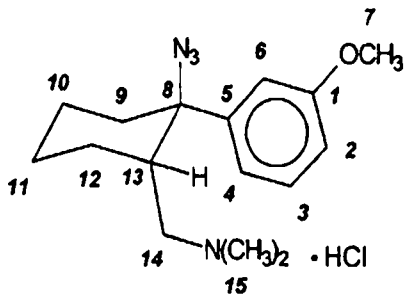
33.4 g of a mixture consisting of 45% (RR,SS) Tramadol hydrochloride and 55% of the corresponding (RS,SR) isomer was immersed in 50 ml trifluoroacetic acid, 5.2 g of sodium azide was added, and the reaction mixture was stirred for 24 hours. The reaction mixture was then evaporated under reduced pressure, 50 ml water was added, and the solution was brought to pH 12 with solid potassium carbonate. The suspension was extracted with 50 ml toluene, the solvent was evaporated and 25 ml hydrogen chloride solution in isopropanol were added. The solution was cooled and filtered. 9.5 g of crude (RR,SS) Tramadol were obtained, and the crude product was purified by recrystallization from isopropanol. The hitherto unknown (RS,SR)-2-(dimethylaminomethyl)-1-azido-1-(3-methoxyphenyl)-cyclohexane hydrochloride was isolated from the reaction mixture, recrystallized from isopropanol and characterized as follows:

ms : 288 m⁺

IR : 2050 cm⁻¹ (N₃)

¹H-NMR (DMSO): 10.42 ppm: (acidic proton); 1H; 7.40-6.90 ppm: (aromatic protons) 4H; 3.79 ppm: (OCH₃), 3H; 2.78, 2.42 ppm: NCH₂, 2H; 2.58, 2.37 ppm: [N(CH₃)₂], 6H; 2.30-1.40 ppm: cyclohexane ring protons, 9H.

¹³C-NMR (DMSO): 159.74 ppm: C₁; 144.12 ppm: C₅; 130.08 ppm: C₃; 117.36 ppm: C₄; 112.97, 111.35 ppm: C₂, C₆; 69.61 ppm: C₈; 59.29 ppm: C₁₄; 55.21 ppm: C₇; 44.6 ppm: C₁₅; 40.12 ppm: C₁₃; 35.94, 27.02, 23.56, 21.63 ppm: cyclohexane ring carbon nuclei.



It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be

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(54) Orale Anwendung von (+)-O-Demethyltramadol als Schmerzmittel

(57) Es wird die Verwendung von (+)-O-Demethyltramadol zur oralen Applikation bei der Behandlung von starken akuten und/oder chronischen Schmerzen beschrieben.

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Beschreibung

Die Erfindung betrifft die orale Anwendung von (+)-O-Demethyltramadol zur Behandlung von starken, akuten und/oder schweren chronischen Schmerzen.

5 Opiode haben in der Schmerztherapie eine unangreifbare Vormachtsstellung bei der Behandlung von schweren Schmerzen (Zenz, M., Jurna I. (1993) Lehrbuch der Schmerztherapie, Wissenschaftliche Verlagsgesellschaft Stuttgart). Dies gilt für die Behandlung von akuten wie auch chronischen Schmerzzuständen, wobei die opioidtypischen Nebenwirkungen wie Atemdepression, Obstipation und insbesondere die bei chronischer Anwendung auftretende Toleranz- und Abhängigkeitsentwicklung in Kauf genommen werden. Die therapeutische Praxis zeigte, dass oral
10 anwendbare Substanzen für die chronische Schmerzbehandlung besonders gut geeignet sind, da sie leicht dosierbar und im Gegensatz zu Injektionspräparaten von Patient und/oder dem Pflegepersonal ohne besonderen Aufwand und ohne Hilfsmittel appliziert werden können (Cherny, N. J. et al., Medikamentöse Therapie von Tumorschmerzen II, Anwendung von Opioiden, Der Schmerz 9, 3 - 19 (1995), Evans, P. J. Opiates in the Management of Chronic Pain in Clinics and Anaesthesiology Vol. 1, No. 1, 71 - 94). Voraussetzung ist, dass die Substanzen eine gute orale Verfügbarkeit und eine ausreichend lange Wirkdauer besitzen. Durch eine lange Wirkdauer, die eventuell auch unter Verwendung
15 von galenischen Hilfsmitteln, wie z. B. Depotzubereitungen, erreichbar ist, kann die Applikationshäufigkeit pro Tag reduziert werden, ohne dass es zu einem Einbruch des für eine optimale Therapie erforderlichen gleichmäßigen Wirkspiegels kommt (Strubelt, O., Pharmakologie, Toxikologie und Verschreibung von Opioiden, Internist 35, 185 - 191 (1994)).

20 Für die Behandlung von schweren chronischen Schmerzzuständen hat sich in den letzten Jahren oral retardiertes Morphin immer stärker durchgesetzt (Zenz et al. (1989), Retardiertes Morphin zur Langzeittherapie schwerer Tumorschmerzen, Dtsch. med. Wschr. 114, 43 - 47; Zenz et al. (1990), Orale Opiattherapie bei Patienten mit „nicht-malignen“ Schmerzen, Der Schmerz 4, 14; Ventafridda et al. (1990), Side-effects and Limits of Long-term Oral Morphin Therapy, in: Treatment of Chronic Pain pp 256 - 269, M. Mumenthaler, P.A. van Zwieten, J. M. Falcot Eds.: Harwood Academic
25 Publishers, Chur (1990)), so dass orale Morphinpräparate heute die Mittel der Wahl darstellen, obwohl Morphin eine Reihe von ungünstigen Eigenschaften besitzt. Ein wesentlicher Nachteil von Morphin besteht in der geringen oralen Verfügbarkeit, die auf einer starken First-pass-Inaktivierung in der Darmwand und bei der Leberpassage beruht. Alters- oder krankheitsbedingte Änderungen in der Metabolisierungskapazität können daher die orale Verfügbarkeit von Morphin verändern und spezielle Dosisanpassungen erforderlich machen, um Fehldosierungen zu vermeiden. Eine wei-
30 tere negative Eigenschaft von Morphin ist die starke opstipierende Nebenwirkung, die bei der oralen Morphintherapie zu Verstopfung führt und obligat den Einsatz von Laxantien erforderlich macht (Cherny et al. 1995 a.a.O.). Eine weitere gravierende Nebenwirkung ist das Auftreten von Toleranz und körperlicher sowie psychischer Abhängigkeit, die eine Unterstellung von Morphin unter die Betäubungsmittelgesetzgebung bedingt.

Die geringe orale Verfügbarkeit von Morphin erfordert eine besondere galenische Aufbereitung, z. B. in retardierenden Formulierungen, um Morphin oral applizierbar zu machen. Diese geringe orale Applizierbarkeit ist insbesondere auf die phenolische Hydroxylgruppe des Morphins zurückzuführen. Auch für viele andere morphinanaloge Verbindungen, wie Nalbuphin, Naloxon, Naltrexon, die ebenfalls eine phenolische Hydroxylgruppe aufweisen, wurde eine geringe
35 orale Anwendbarkeit nachgewiesen.

Die der Erfindung zugrunde liegende Aufgabe bestand deshalb in der Bereitstellung einer Verbindung, die in einem Arzneimittel bei starken akuten und/oder chronischen Schmerzen oral applizierbar ist und die eine mit Morphin vergleichbare Wirkstärke aufweist, ohne dessen Nebenwirkungen zu besitzen.

Überraschenderweise wurde gefunden, dass das (+)-Enantiomer des O-Demethyltramadol und seine physiologisch verträglichen Salze eine hervorragende Wirkstärke besitzen und demzufolge eine hohe analgetische Wirkung aufweisen und trotz einer phenolischen Hydroxylgruppe wesentlich besser oral verfügbar als bekannte opioidanaloge
45 Verbindungen sind. Damit wird eine geringere Applikationsdosis verbunden mit einer größeren Dosierungssicherheit ermöglicht.

Darüber hinaus haben tierexperimentelle Befunde gezeigt, dass das (+)-Demethyltramadol schwächere obstipierende Wirkungen als Morphin besitzt. Außerdem ist die Gefahr, daß bei einer Dauerbehandlung eine psychische Abhängigkeit ausgebildet wird, geringer als bei Morphin.

50 Die gute orale Verfügbarkeit und analgetische Wirksamkeit des als Wirkstoff in einem Arzneimittel erfindungsgemäß verwendeten (+)-O-Demethyltramadols wurde in Analgesietests an Maus und Ratte nachgewiesen.

Die pharmakologischen Untersuchungen wurden wie folgt geführt:

Analgesieprüfung im Writhing-Test an der Maus

55 Die Untersuchung auf analgetische Wirksamkeit wurde im Phenylcholin-induzierten Writhing an der Maus (modifiziert nach I. C. Hendershot, J. Forsaith, J. Pharmacol. Exp. Ther. 125, 237 - 240 (1959)) durchgeführt. Dazu wurden männliche NMRI-Mäuse mit einem Gewicht von 25 bis 30 g verwendet. Gruppen von 10 Tieren pro Substanzdosis

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erhielten 10 Minuten nach intravenöser Gabe und 30 Minuten nach oraler Gabe der erfindungsgemäß zu verwenden-
den Verbindungen 0,3 ml/Maus einer 0,02 %-igen wäßrigen Lösung des Phenylchinon (Phenylbenzochinon, Fa.
Sigma, Deisenhofen; Herstellung der Lösung unter Zusatz von 5 % Ethanol und Aufbewahrung im Wasserbad bei 45°
C) intraperitoneal appliziert. Die Tiere wurden einzeln in Beobachtungskäfige gesetzt und mittels Drucktastenzähler die
5 Anzahl der Schmerz-induzierten Streckbewegungen (sogenannte Writhing-Reaktionen = Durchdrücken des Körpers
nach Abstrecken der Hinterextremitäten) 5 bis 20 Minuten nach der Phenylchinongabe ausgezählt. Aus der dosisab-
hängigen Abnahme der Writhing-Reaktionen im Vergleich zu parallel untersuchten, nur mit Phenylchinon behandelten
Kontrollgruppen wurden mittels Regressionsanalyse (Auswerteprogramm Martens, EDV-Serivce, Eckental) der ED₅₀-
Wert für die Hemmung der Writhing-Reaktion berechnet.

Analgesieprüfung im Tail-Flick-Test an Ratte und Maus

Die analgetische Wirksamkeit der erfindungsgemäß zu verwendenden Verbindung wurde im Wärmestrahlflick-Test (Tail-
Flick-Test) an Maus und Ratte nach der Methode von D'Amour und Smith (J. Pharm. Ex. Ther. 72, 74 - 79 (1941)) unter-
15 sucht. Dazu wurden männliche NMRI-Mäuse mit einem Gewicht von 20 bis 25 g oder weibliche Sprague Dawley-Ratten
mit einem Gewicht von 120 bis 160 g verwendet. Die Tiere wurden einzeln in Testkäfige gesetzt und die Schwanzbasis
einem fokussierten Wärmestrahlflick einer elektrischen Lampe (Rhema-Analgesiemeter) ausgesetzt. Die Lampenintensität
wurde so eingestellt, daß die Zeit vom Einschalten der Lampe bis zum plötzlichen Wegzucken des Schwanzes
(Schmerzlatenz) bei unbehandelten Tieren 3 bis 6 Sekunden betrug. Vor Gabe der erfindungsgemäß zu verwendenden
20 Verbindung wurden die Tiere innerhalb von 5 Minuten zweimal getestet und der Mittelwert dieser Messungen als Vor-
testmittelwert berechnet. Die Schmerzmessung wurde 20, 40 und 60 Minuten nach intravenöser und 30, 60, 90, 120
Minuten nach oraler Gabe durchgeführt. Bei Anstieg der Schmerzlatenz wurde die maximale Expositionszeit auf 12
Sekunden beschränkt und die Zunahme der Latenzzeit von >150 % des Vortestmittelwerts als analgetische Wirkung
gewertet. Zur Bestimmung der Dosisabhängigkeit wurden die Verbindungen in 3 bis 5 logarithmisch ansteigenden
25 Dosen, die jeweils die Schwellen- und die maximale Wirkdosis einschlossen, appliziert und aus der Anzahl der Tiere,
die analgetische Wirkung zeigten, nach der Methode von Litchfield und Wilcoxon (J. Pharm. Ex. Ther. 96, 99 bis 113
(1949)) die ED₅₀-Werte bestimmt. Die ED₅₀-Berechnung erfolgte im Wirkmaximum jeweils 20 Minuten nach intravenö-
ser und jeweils 30 Minuten nach oraler Substanzgabe.

Die Bestimmung der oralen Wirkverfügbarkeit erfolgte aus dem Verhältnis der ED₅₀-Werte bei i.v.- und p.o.-Gabe.

Wirkverfügbarkeit = $\frac{ED_{50} \text{ i.v.}}{ED_{50} \text{ p.o.}}$

Tabelle 1

Analgetische Wirksamkeit und orale Wirkverfügbarkeit von Morphin und (+)-O-Demethyltramadol		
Versuchsmodell	ED ₅₀ -Werte (mg/kg)	
	(+)-O-Demethyltramadol	Morphin
Tail-flick, Maus i.v.	1,41	1,05
Tail-flick, Maus p.o.	3,75	18,90
orale Wirkverfügbarkeit	0,38	0,06
Writhing, Maus i.v.	0,49	0,33
Writhing, Maus p.o.	1,87	4,70
orale Wirkverfügbarkeit	0,26	0,07
Tail-flick, Ratte i.v.	1,01	0,93
Tail-flick, Ratte p.o.	4,90	75,00
orale Wirkverfügbarkeit	0,21	0,01

Das erfindungsgemäß verwendende (+)-Demethyltramadol zeigte im Writhing-Test an der Maus und im Tail-Flick-Test an der Ratte eine ausgeprägte analgetische Wirkung. Während bei Morphin der Faktor für die orale Wirkver-

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Orale Retard-Präparation enthaltend Tramadol sowie Verfahren zu ihrer Herstellung

(57)

Bei einer oralen Retard-Präparation in Form von Tabletten oder Filmtabletten mit verzögerter Wirkstoffabgabe ist als Wirkstoff Tramadolhydrochlorid in einer Menge von 15 bis 80 Gew.% und als Matrixbildner ein Fettalkohol, wie z.B. n-Hexadecanol (Cetylalkohol) in einer Menge von 20 bis 60 Gew.% jeweils bezogen auf das Tablettengewicht, Rest Tablettenhilfsstoffe und Füllstoffe, wie z.B. mikrokristalline Cellulose, Milchkucker, Gleit-, Schmier- und Fließregulierungsmittel, wie z. B. hochdisperses Siliziumdioxid, Magnesiumstearat oder Talk in Mengen von 0 bis 65 Gew.% eingesetzt. Bei dem Verfahren zur Herstellung der oralen Retard-Präparation wird der Wirkstoff mit mikrokristalliner Cellulose vermischt und mit der in Isopropanol gelösten Fettalkoholmatrix besprüht, worauf das erhaltene fließfähige Granulat zu Tabletten verpreßt wird und anschließend der Filmüberzug aufgebracht wird.

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Beschreibung

[0001] Die Erfindung bezieht sich auf eine orale Retard-Präparation in Form von Tabletten oder Filmtabletten mit verzögerter Wirkstoffabgabe sowie ein Verfahren zu ihrer Herstellung.

[0002] Matrixfilmtabletten zur peroralen Anwendung, welche Wirkstoffe in einer Weise enthalten, daß dieser nach Einnahme so stark verzögert aus der Tablettenmatrix freigesetzt wird, daß eine einmal tägliche Einnahme ausreicht, um therapeutisch relevante Blutplasmakonzentrationen aufrechtzuerhalten, sind prinzipiell bekannt.

[0003] Tramadolhydrochlorid-(R,R,SS)-2-(Dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol hydrochlorid - ist nach dem WHO-Stufenplan ein mittelstarkes Schmerzmittel der Stufe 2 und wird seit vielen Jahren erfolgreich in der Therapie von Schmerzen eingesetzt. Bislang befinden sich am Markt nur pharmazeutische Zubereitungen, die diesen Wirkstoff einer therapeutischen Anwendung unretardiert in Form von Tropfen, Ampullen, Zäpfchen, Kapseln etc. zugänglich machen, was für den Patienten eine mehrmals tägliche Verabreichung bzw. Einnahme bedeutet, um eine ausreichende Schmerzstillung aufrechtzuerhalten.

[0004] Vor kurzer Zeit erfolgte auch die Markteinführung einer retardierten Tramadol HCl Arzneiform (Filmtabletten) in drei verschiedenen Wirkstärken (100, 150 und 200 mg), die zur zweimal täglichen Einnahme geeignet ist. Die entsprechende Präparation ist beispielsweise in der EP-A2 642 788 beschrieben. Bei dieser bekannten für die zweimal tägliche Verabreichung geeigneten Darreichungsform wird ein feuchtigkeitsunempfindliches, physiologisch verträgliches Tramadolsalz (Tramadol HCl) mit mindestens einem Celluloseether und/oder Celluloseester, der in einer 2 gew. %igen wäßrigen Lösung bei 20° C eine Viskosität zwischen 3000 und 150000 mPas aufweist, als Matrixbildner verwendet.

[0005] Das Trägermaterial ist in den angeführten Beispielen zu 14 bis 34 Gew.% enthalten und bewirkt, daß in vitro nach 5 Stunden etwa 69 bis 89 % und längstens nach 12 Stunden 100 % des in der Tablette enthaltenen Wirkstoffes freigesetzt wird. Das bedeutet, daß mit dieser Formulierung die Freisetzung des genannten, gut wasserlöslichen Wirkstoffes nicht lange genug verzögert werden kann, um für eine 1 x tägliche Einnahme einen ausreichend hohen, analgetisch wirksamen Blutplasmaspiegel aufrechtzuerhalten.

[0006] Überraschenderweise wurde nun gefunden, daß bei Wahl einer geeigneten Matrix und bei Wahl einer geeigneten Zusammensetzung die Formulierung so gestaltet werden kann, daß tatsächlich mit nur einmal täglicher Verabreichung das Auslangen gefunden werden kann. Die Erfindung zielt nun darauf ab, eine derartige Formulierung bereit zu stellen, mit welcher der Wirkstoff Tramadolhydrochlorid bei einmaliger täglicher Darreichung einen ausreichend hohen analgetisch wirksamen Blutplasmaspiegel aufrechtzuerhalten erlaubt. Zur Lösung dieser Aufgabe besteht die erfindungsgemäße orale Retard-Präparation im wesentlichen darin, daß als Wirkstoff Tramadolhydrochlorid in einer Menge von 15 bis 80 Gew.% und als Matrixbildner ein Fettalkohol, wie z.B. n-Hexadecanol (Cetylalkohol) in einer Menge von 20 bis 60 Gew.% jeweils bezogen auf das Tablettengewicht, Rest Tablettenhilfsstoffe und Füllstoffe, wie z.B. mikrokristalline Cellulose, Milchzucker, Gleit-, Schmier- und Fließregulierungsmittel, wie z.B. hochdisperses Siliziumdioxid, Magnesiumstearat oder Talk in Mengen von 0 bis 65 Gew.% eingesetzt ist. Dadurch, daß nun n-Hexadecanol als Matrixbildner verwendet wurde, wurde nun überraschenderweise gefunden, daß gegenüber dem bekannten Celluloseether- und/oder Celluloseestermatrizes eine deutliche Vergleichmäßigung der Freisetzung über 24 Stunden erzielt werden kann und daß tatsächlich gleichzeitig nicht nur die Freisetzung über 24 Stunden vergleichmäßig werden konnte, sondern daß auch über diesen gesamten Zeitraum eine hinreichend hohe Plasmakonzentration aufrechterhalten werden kann. Die wasserunlösliche Fettalkoholmatrix hat hierbei darüberhinaus den Vorzug, die Freisetzung weitestgehend unabhängig vom pH-Wert in über 24 Stunden ausreichender und gleichmäßiger Weise sicherzustellen. Gleichzeitig hat diese Fettalkoholmatrix gegenüber bekannten Zubereitungen den Vorteil, daß der Wirkstoff unmittelbar in die Matrix eingearbeitet werden kann und in der Folge eine Filmtablette hergestellt werden kann, wodurch sich die Herstellung der Zubereitung wesentlich vereinfacht. Die Filmabdeckung dient hierbei in erster Linie der Geschmacksabdeckung.

[0007] Mit Vorteil ist die erfindungsgemäße Formulierung hierbei so getroffen, daß der Wirkstoff in Mengen von 25 bis 45 Gew.%, der Matrixbildner in Mengen von 25 bis 55 Gew.% und Tablettenhilfsstoffe in Mengen von 0,5 bis 40 Gew.% vorliegen, wobei vorzugsweise der Wirkstoff in Mengen zwischen 50 und 800 mg, vorzugsweise 200 bis 400 mg, je Tablette vorliegt.

[0008] Wie bereits eingangs erwähnt, hat die Verwendung von Fettalkohol zur Folge, daß die Wirkstofffreisetzung pH-unabhängig und gleichmäßig über einen hinreichend langen Zeitraum gewährleistet ist, welcher mit bisherigen Formulierungen nicht ohne weiteres erzielt werden konnte. Vergleichsversuche mit Celluloseether und Celluloseestern sowie Eudragit haben durchwegs bestätigt, daß mit diesen bekannten Matrixbildnern das erfindungsgemäße Ziel, eine einmal tägliche Einnahme bei gleichzeitig ausreichend hohem analgetisch wirksamen Blutplasmaspiegel aufrechtzuerhalten, nicht gelingt.

[0009] Mit Rücksicht auf den bitteren Geschmack von Tramadolhydrochlorid ist, wie bereits zuvor erwähnt, eine Geschmacksabdeckung wünschenswert. Mit Vorteil ist die Ausbildung hierbei so getroffen, daß die Tabletten mit einem geschmacksabdeckenden wasserlöslichen Filmüberzug, wie z.B. Hydroxypropylmethylcellulose in Kombination mit

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Poly(meth)acrylaten, Polyethylenglykolen, Talk und Farbpigmenten, versehen sind.

[0010] Im Rahmen der erfindungsgemäßen Formulierung sind diejenigen Formulierungen besonders bevorzugt, bei welchen die Tabletten eine in vitro Wirkstoff-Freisetzung von 5 bis 35 Gew.% nach 1 h, 15 bis 45 Gew.% nach 2 h, 35 bis 75 Gew.% nach 6 h, 60 bis 90 Gew.% nach 12 h, 70 bis 98 Gew.% nach 18 h und 80 bis 100 Gew.% nach 24 h aufweisen.

[0011] Trotz der üblicherweise in hohem Maße vom pH-Wert abhängigen Freisetzungsgeschwindigkeit von Wirkstoffen gelingt es mit der Wahl von Cetylalkohol bzw. n-Hexadecanol eine Matrix zu schaffen, bei welchem die Freisetzungsgeschwindigkeit weitestgehend vom pH-Wert unabhängig wird. Der pH-Wert schwankt während der Passage eines Arzneimittels durch den Verdauungstrakt z. B. in Abhängigkeit von der Nahrungsaufnahme und kann Werte zwischen 1 und 7,5 erreichen. Für die gewünschte Langzeit Retardwirkung über einen Zeitraum von 24 Stunden ist daher die Auffindung einer geeigneten Matrix, bei welcher die Abgabe des Wirkstoffes aus der Formulierung im Gastrointestinaltrakt unabhängig vom jeweils vorherrschenden pH-Milieu erfolgt von besonderer Bedeutung.

[0012] Das erfindungsgemäße Verfahren zur Herstellung dieser oralen Retard-Präparation ist dadurch gekennzeichnet, daß der Wirkstoff mit mikrokristalliner Cellulose vermischt und mit der in Isopropanol gelösten Fettalkoholmatrix besprüht wird, worauf das erhaltene fließfähige Granulat zu Tabletten verpreßt wird und anschließend der Filmüberzug aufgebracht wird, wodurch sich eine besondere einfache Herstellung ergibt.

[0013] Die Erfindung wird nachfolgend anhand von Ausführungsbeispielen näher erläutert.

Beispiel 1

[0014] Matrixtabletten entsprechend nachfolgender Rezeptur pro Filmtablette

Tablettenkern:	
Tramadolhydrochlorid	300,0 mg
Cetylalkohol	345,5 mg
Mikrokristalline Cellulose	250,0 mg
Magnesiumstearat	4,5 mg
Filmhülle:	
Macrogol 6000	3,286 mg
Hydroxypropylmethylcellulose	2,738 mg
Titandioxid	3,296 mg
Talk	9,858 mg
Poly(ethylacrylat,methylmethacrylat)2:1	0,822 mg

wurden in einer Ansatzgröße von 2000 Filmtabletten in folgender Weise produziert:

[0015] Der Wirkstoff wurde in einem Aeromatic-Strea 1-Wirbelschichtgranulator zusammen mit der mikrokristallinen Cellulose vorgemischt und mit einer isopropanolischen Lösung des Cetylalkohols besprüht, sodaß nach dem Sieben durch ein 1,25 mm Sieb ein homogenes, gut fließfähiges Granulat erhalten wurde.

[0016] Dieses wurde in einem Turbulamischer mit dem Magnesiumstearat 5 Minuten gemischt und anschließend auf einer Fette Rundlaufablettenpresse mit Oblong-Stempeln im Format 21 x 7,5 mm zu Tabletten mit einem Gewicht von 900 mg je Tablette verpreßt.

[0017] Die Befilmung erfolgte durch Aufsprühen einer wäßrigen Suspension in der oben angeführten Zusammensetzung nach dem in der Pharmaindustrie üblichen Dragierkesselverfahren.

[0018] Die in vitro Freisetzung des Wirkstoffes Tramadolhydrochlorid aus der Matrixtablette wurde nach Ph.Eur. 3rd ed. 1997 mittels Blattrührerapparatur bestimmt. Die Temperatur des Lösungsmediums betrug 37 ± 0,5° C und die Rotationsgeschwindigkeit des Rührers 100 Umdrehungen pro Minute. Als Prüfmedien dienten wahlweise

- a.) 1000 ml 0,1 N Salzsäure, pH = ca. 1,2
- b.) 750 ml 0,1 N Salzsäure, pH = ca. 1,2 während der ersten beiden Stunden, ab der dritten Stunde Zusatz von 250 ml 0,2 M Na₃PO₄-lösung mit pH-Einstellung auf 6,8
- c.) 1000 ml Phosphat-Citrat Puffer, pH = 6,8 nach Ph.Eur.

[0019] Die zum jeweiligen Zeitpunkt aus der Matrixtablette freigesetzte, im Prüfmedium gelöste Wirkstoffmenge wurde mittels Spektrofotometrie bestimmt. Es wurden die in nachfolgender Tabelle angeführten Freisetzungswerte (Mit-

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, DC, 17 de noviembre de 2005

Apoderado: Alicia Lloreda Ricaurte

Oficio: 11000

ASUNTO Radicación: 00-74927
 Trámite 002
 Evento 001
 Actuación 430
 Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

- ◆capitulo descriptivo, folios 5 a 30;
- ◆capitulo reivindicatorio, folios 119 y 120;
- ◆1° examen de forma, folios 40 y 41;
- ◆respuesta técnica al 1° examen de forma, folios 76 a 79;
- ◆2° examen de forma, folio 133;
- ◆solicitud de la cual se reivindica prioridad y la traducción exigida, folios 52 a 108;
- ◆ solicitud del examen de patentabilidad, folios 135 a 137.

Objeto de la invención:

El título de la invención "USO DE (+)TRAMADOL Y/O (+)-O-DEMETILTRAMADOL, O-DESMETIL-N-MONODESMETIL-TRAMADOL PARA LA PREPARACIÓN DE UN MEDICAMENTO PARA EL TRATAMIENTO DE URGENCIA URINARIA INCREMENTADA O INCONTINENCIA URINARIA, Y MEDICAMENTOS QUE LOS CONTIENEN".

Es el uso de cualquier medicamento caracterizado porque contiene como sustancia activa almenos (+)-tramadol en forma de base libre y/o en forma de sales fisiológicamente tolerables y eventuales aditivos y/o excipientas.

El campo de la invención, según la Clasificación Internacional de Patentes: A61K 31/135

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Se realizó la búsqueda del estado de la técnica con fecha anterior a la fecha de presentación de la primera solicitud, de la cual se reivindica prioridad, 05 de octubre-1999. Consultada la fuente de información con que cuenta este despacho se encontró muchos documentos solo se adjuntaron algunos:

No.	Documento No.	Título	*Fecha de Publicación
D1	US3652589	1-(m-substituted phenyl)-2-aminomethyl cyclohexanols	28-mar-1972
D2	EP0546676	Composition comprising o tramadol material and a non-steroidal anti-inflammatory drug	16-jun-1992
D3	WO9304675	Composition comprising a tramadol material and acetaminophen and its use	18-mar-1993
D4	EP0642788	Tramadolsalz enthaltende arzneimittel mit verzögerten wirkstofffreisetzung	15-mar-1993
D5	WO9717948	Formulation for respiratory tract administration	22-may-1997
D6	EP0831082	Process for purification of (RR-SS)-2-dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexanol hydrochloride	25-mar-98

D7	EP0870499	Orale anwendung von(+)-o-demethyltramadol als schmerzmittel	14-oct-1998
D8	EP0914823	Orale retard-präparation enthaltend tramadol sowie verfahren zu ihrer herstellung	12-may-

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”*

En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica.” “El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40.”

La solicitud en estudio reclama como nuevo un medicamento caracterizado porque contiene como sustancia activa almenos (+)-tramadol en forma de base libre y/o en

forma de sales fisiológicamente tolerables y eventuales aditivos y/o excipientes.

Dado que el objeto de las reivindicaciones 1 a 6 son realmente el uso tácito del tramadol y sus sales porque realmente como medicamento no esta definido en características técnicas, o sea no esta definido técnicamente, con las sustancias constitutivas, y tal como esta definido el medicamento no es nuevo e inventivo “per se” ya que se refiere a medicamentos convencionales o de analogia conocidos universalmente (principio activo + excipientes) en el estado de la técnica, y su patentabilidad esta ligada unicamente a la patentabilidad del princpio activo. Ya que técnicamente como medicamento es lo convencional y tal como se dijo su patentabilidad solo reside en la novedad del tramadol y sus sales farmaceuticamente aceptables, siendo que la solicitud describe es solamente un nuevo uso.

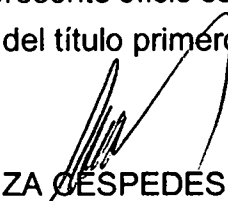
-Los documentos que solo se citaron D1 a D8, contienen el tramadol base, la sal HCl, (+)-tramadol, (+)-o-demetiltramadol y sus sales, al igual que los procesos de síntesis y los medicamentos que los comprenden, además de contener formas farmceuticas específicas. Por lo cual se observa que la presente solicitud no tiene novedad.

Cuando una solicitud esta afectada su novedad, obviamente no posee nivel inventivo. En conclusión los requisitos de Patentabilidad de la presente solicitud **están** afectadas así:

Documento	Reivindicaiones	Requisito que afecta
D1	1 a 6	Novedad
D2	1 a 6	Novedad
D3	1 a 6	Novedad
D4	1 a 6	Novedad
D5	1 a 6	Novedad
D6	1 a 6	Novedad
D7	1 a 6	Novedad
D8	1 a 6	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2,literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
24 NOV. 2005

CONCEPTO TÉCNICO No. 1859	EXAMINADOR TÉCNICO Código No.202012
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