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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 538

Referencia : Expediente No. 07.079.189
Asunto : Solicitud de patente para **USO DE INHIBIDORES DE TIROSINA QUINASA PARA EL TRATAMIENTO DE RINOSINUSITIS CRONICA**
Solicitante : **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
Clase : A61K 031/517, A61P 011/000
Publicada en : La Gaceta No. 591 del 30 de abril de 2008
Fecha de Solicitud : 2 de agosto de 2007

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$ 420.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44372 de 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

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No. M-2008-136853\SDC

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Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-79189

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 591 DE

FECHA 30 DE ABRIL DE 2008 EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL 30 DE JULIO DE 2008

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

(19) **United States**(12) **Patent Application Publication** (10) Pub. No.: **US 2003/0149062 A1****Jung et al.** (43) Pub. Date: **Aug. 7, 2003**(54) **USE OF TYROSINE KINASE INHIBITORS
FOR THE TREATMENT OF
INFLAMMATORY PROCESSES**(75) Inventors: **Birgit Jung, Laupheim (DE); Hubert
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& Co. KG, Ingelheim (DE)**(21) Appl. No.: **10/353,616**(22) Filed: **Jan. 29, 2003**(30) **Foreign Application Priority Data**

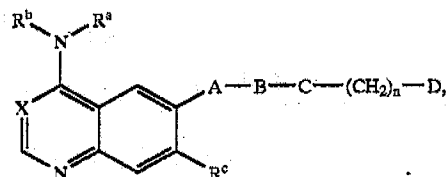
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Publication Classification(51) Int. Cl.⁷ **A61K 31/517; A61K 31/4709;
A61K 31/55**(52) U.S. Cl. **514/266.22; 514/314; 514/313;
514/266.24; 514/266.4; 514/217.06**(57) **ABSTRACT**

A method of treating inflammatory diseases of the airways or intestines which comprises administering substances selected from the group consisting of:

(a) quinazolines of general formula

(I)

wherein A, B, C, D, X, R^a, R^b, R^c and n are as defined herein,

(b) the compounds

- (1) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-dimethylamino-cyclohexyl)amino]-pyrimido[5,4-d]pyrimidine,
- (2) 4-[(R)-(1-phenylethyl)amino]-6-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine, and
- (3) 4-[[3-chloro-4-(3-fluoro-4-benzyloxy)-phenyl]amino]-6-[[[(2-methanesulphonyl-ethyl)amino]methyl]-furan-2-yl]quinazoline or

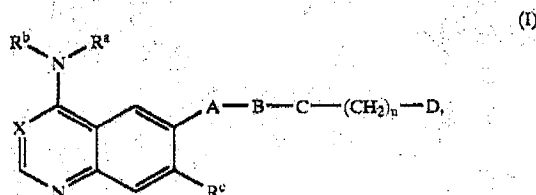
(d) the antibodies Cetuximab C225, Trastuzumab, ABX-EGF and Mab ICR-62, and

(f) EGFR-antisense.

USE OF TYROSINE KINASE INHIBITORS FOR THE TREATMENT OF INFLAMMATORY PROCESSES

DESCRIPTION OF THE INVENTION

[0001] The present invention relates to the use of quinazolinines of general formula



[0002] wherein A, B, C, D, X, R^a, R^b, R^c and n are defined below, or

[0003] the compounds

[0004] (1) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-dimethylamino-cyclohexyl)amino]-pyrimido [5,4-d] pyrimidine,

[0005] (2) 4-[(R)-(1-phenylethyl)amino]-6-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine,

[0006] (3) 4-[[3-chloro-4-(3-fluoro-4-benzyloxy)-phenyl]amino]-6-(5-[(2-methanesulphonyl-ethyl)amino]methyl)-furan-2-yl]quinazoline or

[0007] the antibody Cetuximab C225, Trastuzumab, ABX-EGF, Mab ICR-62 or EGFR-antisense,

[0008] the tautomers, stereoisomers and salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, for preparing a pharmaceutical composition for the prevention and treatment of

[0009] diseases of the airways or lungs which are accompanied by increased or altered production of mucus, such as e.g. inflammatory diseases of the airways such as acute bronchitis, chronic bronchitis, chronic obstructive bronchitis (COPD), asthma, bronchiectasis, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α 1-antitrypsin deficiency, coughs, lung emphysema, pulmonary fibrosis or hyperreactive airways.

[0010] Moreover, the compounds are also suitable for the treatment of inflammatory diseases of the gastro-intestinal tract or bile duct or gall bladder which are accompanied by impaired tyrosine kinase function, such as may be found for example in acute or chronic inflammatory changes such as cholecystitis, Crohn's disease, ulcerative colitis, ulcers or polyposis in the gastro-intestinal tract or such as occur in diseases of the gastro-intestinal tract which are associated with increased secretion, such as Ménétrier's disease, secreting adenomas or protein loss syndrome,

[0011] and also for the treatment of inflammatory diseases of the joints, such as rheumatoid arthritis, inflammatory diseases of the skin and the eyes, inflammatory pseudopolyps, in colitis cystica profunda or in pneumatosis cystoides intestinalis.

[0012] Preferred fields of application are inflammatory diseases of the respiratory tract or bowel, such as chronic bronchitis (COPD), chronic sinusitis, asthma, Crohn's disease, ulcerative colitis or polyposis of the intestines.

[0013] Particularly preferred fields of application are inflammatory diseases of the airways or lungs such as chronic bronchitis (COPD) or asthma.

[0014] In the above general formula (I)

[0015] X denotes a nitrogen atom or a carbon atom substituted by a cyano group,

[0016] R^a denotes a hydrogen atom or a C₁₋₄-alkyl group,

[0017] R^b denotes a phenyl, benzyl or 1-phenylethyl group, wherein the phenyl nucleus may be substituted in each case by the groups R¹ and R², while

[0018] R¹ and R², which may be identical or different, in each case denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

[0019] a C₁₋₄-alkyl, hydroxy, C₁₋₄-alkoxy, C₃₋₆-cycloalkyl, C₄₋₆-cycloalkoxy, C₂₋₅-alkenyl or C₂₋₅-alkynyl group,

[0020] an aryl, aryloxy, arylmethyl or arylmethoxy group,

[0021] a C₃₋₅-alkenyloxy or C₃₋₅-alkynyloxy group, while the multiple bond is isolated from the oxygen atom,

[0022] a C₁₋₄-alkylsulphenyl, C₁₋₄-alkylsulphinyl, C₁₋₄-alkylsulphonyl, C₁₋₄-alkylsulphonyl-oxy, trifluoromethylsulphenyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

[0023] a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

[0024] an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

[0025] a cyano or nitro group or an amino group optionally substituted by one or two C₁₋₄-alkyl groups, while the substituents may be identical or different,

[0026] A denotes an oxygen atom or an imino group optionally substituted by a C₁₋₄-alkyl group,

[0027] B denotes a bond, a carbonyl or sulphonyl group,

[0028] C denotes a methylene, ethylene or ethenylene group,

[0029] n denotes one of the numbers 0 or 1,

[0030] D denotes an amino, C₁₋₄-alkylamino, C₃₋₅-cycloalkylamino or di-(C₁₋₄-alkyl)-amino or di-(C₃₋₅-cycloalkyl)-amino group wherein the alkyl and cycloalkyl moieties may be identical or different,

[0031] a C₂₋₄-alkylamino group wherein the alkyl moiety is substituted in the β , γ or δ position to the nitrogen atom of the amino group by the group R³, while

[0032] R³ denotes a hydroxy, C₁₋₄-alkoxy, C₁₋₃-alkoxycarbonyl, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group,

- [0205] (2) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- [0206] (3) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-(2-{4-[(S)-(2-oxo-tetrahydrofuran-5-yl)-carbonyl]-piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline,
- [0207] (4) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- [0208] (5) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-[(ethoxycarbonyl)methyl]amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropyl-methoxy-quinazoline,
- [0209] (6) 4-[(R)-(1-phenyl-ethyl)amino]-6-[(4-(morpholin-4-yl)-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline and
- [0210] (7) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-yl)-propyloxy]-7-methoxy-quinazoline
- [0211] or their salts are to be regarded as particularly preferred.
- [0212] The present invention further relates to a process for the treatment of
- [0213] diseases of the airways or lungs which are accompanied by increased or altered production of mucus, such as e.g. inflammatory diseases of the airways such as acute bronchitis, chronic bronchitis, chronic obstructive bronchitis (COPD), asthma, bronchiectasis, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α 1-antitrypsin deficiency, or coughs, lung emphysema, pulmonary fibrosis and hyperreactive airways,
- [0214] for the treatment of inflammatory diseases of the gastrointestinal tract and the bile duct and gall bladder which are accompanied by impaired tyrosine kinase function, such as may be found for example in acute or chronic inflammatory changes such as cholecystitis, Crohn's disease, ulcerative colitis, as well as ulcers and polyposis in the gastro-intestinal tract or such as occur in diseases of the gastro-intestinal tract which are associated with increased secretion, such as Ménétrier's disease, secreting adenomas and protein loss syndrome,
- [0215] and also for the treatment of inflammatory diseases of the joints, such as rheumatoid arthritis, inflammatory diseases of the skin and the eyes, inflammatory pseudopolyps, as well as colitis cystica profunda and pneumatosis cystoides intestinalis, comprising administering an effective amount of one or more of the abovementioned compounds of general formula (I) according to the invention or optionally one of the physiologically acceptable salts thereof to a patient requiring such treatment.

[0216] Preferred and particularly preferred embodiments of the process according to the invention correspond to the embodiments mentioned above for use according to the invention, in terms of the particular compounds and indications.

[0217] In the process according to the invention the abovementioned compounds are used in dosages of 0.001-10 mg/kg of body weight, preferably 0.01-1.5 mg/kg, conveniently administered 1 to 3 times a day.

[0218] The active substances may be administered by oral, buccal or parenteral route, by inhaling sprays, or by rectal or topical application. They may be administered parenterally by subcutaneous, intravenous and intramuscular injections and infusion techniques.

[0219] For this purpose, conventional formulations may be used, such as the preparations mentioned hereinbefore for the active substances. For example, the active substances, optionally combined with other active substances, may be formulated with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

[0220] The active substances may be administered orally in a wide variety of different dosage forms, for example they may be formulated together with different pharmaceutically acceptable inert carriers in the form of tablets, capsules, pastilles, lozenges, hard sweets, powders, atomisers, aqueous suspensions, elixirs, syrups and the like. Such carriers include for example solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. In addition, oral formulations of this kind may be suitably sweetened and/or flavoured with various agents conventionally used for this purpose. In general, the active substances are present in oral formulations of this kind at concentration levels ranging from about 0.5 wt. % to about 90 wt. %, based on the total composition, in amounts sufficient to produce the desired dosage units. Other suitable dosage forms for the active substances comprise formulations for controlled release and devices which are well known to the specialists in the field.

[0221] For the purposes of parenteral administration, solutions of the active substances in sesame or groundnut oil or in aqueous propyleneglycol may be used, as well as sterile aqueous solutions of the corresponding pharmaceutically acceptable salts. Such aqueous solutions should if necessary be suitably buffered and the liquid diluent made isotonic with sufficient salt or glucose. These specific aqueous solutions are particularly suitable for intravenous, intramuscular and subcutaneous injections. In connection with this, the sterile aqueous media used may easily be obtained using common methods well known in the art. For example, distilled water is normally used as the liquid diluent, and the final preparation is passed through a suitable bacterial filter such as a filter made of sintered glass or kieselguhr or unglazed porcelain. Preferred filters of this kind include the Berkefeld, Chamberland and asbestos disc metal Seitz filter, in which the fluid is sucked into a sterile container by means of a suction pump. During the preparation of these injectable solutions the necessary process steps should be taken at all times to ensure that the end products are obtained in a sterile condition. For the purposes of transdermal administration, the dosage form of the particular compound or compounds

may comprise, for example, solutions, lotions, ointments, creams, gels, suppositories, formulations for continuous speed-limited release and equipment for this purpose. Such dosage forms comprise the particular compound or compounds and may contain ethanol, water, penetration promoters and inert carriers such as gel producers, mineral oil, emulsifiers, benzylalcohol and the like.

[0222] The compounds are administered by inhalation in the form of powdered preparations with lactose and other excipients or in the form of aqueous solutions as aerosols.

[0223] The inhalable powders which may be used within the scope of the invention may contain the active substance or combination of active substances either on their own or in admixture with suitable physiologically acceptable excipients. If the active substance or combination of active substances is present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare these inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose), oligo- and polysaccharides (e.g. dextrans), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose, particularly but not exclusively in the form of the hydrates thereof, is preferred. Lactose is particularly preferred, while lactose monohydrate is most preferred, as the excipient according to the invention.

[0224] The propellant-containing aerosols for inhalation which may be used within the scope of the use according to the invention may contain the active substance or combination of active substances dissolved in the propellant gas or in dispersed form. The propellant gases which may be used to prepare the aerosols for inhalation are known from the prior art. Suitable propellant gases are selected from among the hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as preferably fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The abovementioned propellant gases may be used on their own or mixed together. Particularly preferred propellant gases are fluorinated alkane derivatives selected from TG134a (1,1,1,2-tetrafluoroethane), TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof.

[0225] The propellant-containing aerosols for inhalation which may be used within the scope of the use according to the invention may further contain additional ingredients such as cosolvents, stabilisers, surfactants, antioxidants, lubricants as well as pH adjusters. All these ingredients are known in the art.

[0226] If the active substance or combination of active substances according to the invention is administered by inhalation in the form of propellant-free solutions or suspensions, aqueous or alcoholic, preferably ethanolic solutions may be used as solvent. The solvent may be exclusively water or it may be a mixture of water and ethanol. The relative proportion of ethanol to water is not restricted, but the maximum limit is preferably up to 70 percent by volume, particularly up to 60 percent by volume and most particularly up to 30 percent by volume. The remaining percent by volume are made up of water. Solutions or suspensions containing the active substance or combination of active substances are optionally adjusted with suitable acids to a

pH of 2 to 7, preferably 2 to 5. This pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids are hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid. Examples of particularly suitable organic acids are: ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid and others. Preferred inorganic acids are hydrochloric acid, sulphuric acid. Of the organic acids ascorbic acid, fumaric acid and citric acid are preferred. If desired, mixtures of the abovementioned acids may also be used, particularly in the case of acids which have other properties, in addition to their acidifying properties, e.g. as flavourings, antioxidants or complexing agents, such as for example citric acid or ascorbic acid. According to the invention, hydrochloric acid is most preferably used to adjust the pH.

[0227] As already mentioned at the beginning, the compounds of general formula (I) and their salts have valuable properties, particularly an anti-inflammatory activity.

[0228] For example the compounds

[0229] A=4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline,

[0230] B=4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,

[0231] C=4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(2,2-dimethyl-6-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,

[0232] D=4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,

[0233] E=4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[bis-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline,

[0234] F=4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

[0235] G=4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline,

[0236] H=4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((S)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

[0237] I=4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline,

[0238] K=4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

[0239] L=4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline and

[0240] M=4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-yl)-propyloxy]-7-methoxy-quinazoline

- (3) 4-[[3-chloro-4-(3-fluoro-4-benzyloxy)-phenyl]amino]-6-(5-[[2-methanesulphonyl-ethyl]amino]methyl)-furan-2-yl]quinazoline,

as well as tautomers and pharmaceutically acceptable salts of one of the foregoing substances,

(c) the antibodies

- (1) Cetuximab C225,
- (2) Trastuzumab, ABX-EGF, and
- (3) Mab ICR-62

(d) EGFR-antisense.

4. The method according to claim 1, wherein the substance administered is selected from the group consisting of:

- ✓ (1) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-(2-{4-[(S)-(2-oxo-tetrahydrofuran-5-yl)-carbonyl]-piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline,
- ✓ (2) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- ✓ (3) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- ✓ (4) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- ✓ (5) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(2,2-dimethyl-6-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline
- ✓ (6) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- ✓ (7) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- ✓ (8) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- ✓ (9) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[N-(2-ethoxycarbonyl)-ethyl]-N-[(ethoxycarbonyl)methyl]amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- ✓ (10) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- ✓ (11) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopentylmethoxy-quinazoline,
- ✓ (12) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-6-methyl-2-oxo-morpholin-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- ✓ (13) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((4-bis-(2-methoxyethyl)-amino)-1-oxo-2-buten-1-yl]amino)-7-cyclopropylmethoxy-quinazoline

- 1.6 ✓ (14) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

- 1.7 ✓ (15) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

- 1.8 ✓ (16) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline,

- 1.9 ✓ (17) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

- 1.10 ✓ (18) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopentylmethoxy-quinazoline,

- 1.11 ✓ (19) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((S)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

- 1.12 ✓ (20) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

- 1.13 ✓ (21) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

- 1.14 ✓ (22) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

- 1.15 ✓ (23) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-[N-(tetrahydrofuran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

- 1.16 ✓ (24) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline,

- 1.17 ✓ (25) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline,

- 1.18 ✓ (26) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopentylmethoxy-quinazoline,

- 1.19 ✓ (27) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[N-cyclopropyl-N-methyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopentylmethoxy-quinazoline,

- 1.20 ✓ (28) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,

- 1.21 ✓ (29) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,

- 1.22 ✓ (30) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-yl)-propyloxy]-7-methoxy-quinazoline,

- 1.23 ✓ (31) 4-[(3-ethynyl-phenyl)amino]-6-bis-(2-methoxy-ethoxy)-quinazoline,

- 1.21-1.24
- ✓(32) 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinyl-carbonyl)amino]-quinazoline,
 - ✓(33) 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-{5-[[2-methanesulphonyl-ethyl]amino]methyl}-furan-2-yl]quinazoline, *(= 13) (3.14.33)*
 - ✓(34) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-dimethylamino-cyclohexyl)amino]-pyrimido[5,4-d]pyrimidine, *(= 14) (3.14.34)*
 - ✓(35) 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, *(= 15) (3.14.35)*

- 1.26 ✓(36) 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-ethoxy-quinoline,

as well as the pharmaceutically acceptable salts of the foregoing,

- (37) Cetuximab,
- (38) Trastuzumab,
- (39) antibody ABX-EGF,
- (40) Mab ICR-62, and
- (41) EGF-R-antisense.

5. The method according to claim 1, wherein the substance administered is selected from the group consisting of:

- (1) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-(2-{4-[(S)-2-oxo-tetrahydrofuran-5-yl]-carbonyl}-piperazin-1-yl)-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline,
- (2) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- (3) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- (4) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- (5) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(2,2-dimethyl-6-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- (6) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (7) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (8) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (9) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N-[2-(ethoxycarbonyl)-ethyl]-N-[(ethoxycarbonyl)methyl]amino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (10) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,

- (11) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopentyloxy-quinazoline,
- (12) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (13) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-bis-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (14) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,
- (15) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (16) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline,
- (17) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (18) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopentyloxy-quinazoline,
- (19) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((S)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (20) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (21) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (22) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (23) 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline,
- (24) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline,
- (25) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline,
- (26) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopentyloxy-quinazoline,
- (27) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino]-7-cyclopentyloxy-quinazoline,
- (28) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,



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D2(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2005/0019411 A1**
Colombo et al. (43) **Pub. Date: Jan. 27, 2005**(54) **POWDER FOR NASAL ADMINISTRATION
OF DRUGS**(86) **PCT No.: PCT/EP02/11628**(76) **Inventors: Paolo Colombo, Parma (IT); Patrizia
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ROSLYN, NY 11576 (US)**(57) **ABSTRACT**(21) **Appl. No.: 10/492,816**(22) **PCT Filed: Oct. 17, 2002**

The present invention concerns drug formulae for nasal administration and insufflators filled with said formula. The present invention also concerns methods for making said formulae available as well as primary particles for obtaining chimerical agglomerates that can be used in said formulae.

POWDER FOR NASAL ADMINISTRATION OF DRUGS

FIELD OF THE INVENTION

[0001] The present invention concerns drug formulae in powder form for nasal administration, insufflators filled with said formulae, and a method for obtaining them. Moreover, the present invention concerns primary particles for the formation of agglomerates contained in the drug formulae for nasal administration.

PRIOR ART

[0002] The present invention concerns the nasal administration of drugs.

[0003] A pharmaceutical product for nasal topical administration, for example a drug intended to "clear" the nose when affected by a cold, is commonly composed of the formula containing the drug and of the insufflator, which deposits the drug in the nasal cavity. The insufflating device and the formula (in liquid or solid form) are therefore both optimised for reciprocal use and each formula must be suitable for the insufflator used.

[0004] A characteristic required in particular from powders for nasal topical administration is that these should be at the same time fine and coarse: fine to favour their deposition in the nose, coarse to favour their introduction and dosage inside the insufflating device. This paradox is typical of all powders for inhaling, whether they be intended for inhaling through the nose or the lungs.

[0005] Despite the difficulties as described above, the need to have new ways of administering drugs in order to obtain an rapid effect without having to resort to injection has encouraged researchers to further explore the possibility of using inhalation not only for topical, but also for systemic administration. In fact, in recent years scientific literature has seen a growing interest in administration by inhalation, through nose or lungs, for drugs with a systemic action. This way in fact allows the absorption even of substances with a high molecular weight, when rapid action is desired. The respiratory epithelium is relatively extensive and the connective tissue below is characterised by a thick capillary network. For this reason the respiratory region of the nose is considered a useful site for an absorption which gives rise to a pronounced systemic effect.

[0006] As is known, the nose is often used for the abuse of psychoactive substances, but officially the administration of drugs through the nasal mucosa to obtain a systemic action is little used. Most of the nasal preparations in fact contain drugs used for a local (topical) effect on the mucosae. Instead, in order to obtain a systemic effect, the nasal means of administration could allow rapid action to be obtained for drugs that are usually administered by mouth. In fact, thanks to the high vascularisation of the nasal mucosa, the plasmatic peak time of the drug is shortened. Moreover the venous blood from the nasal cavities flows directly into the systemic circle, avoiding a possible effect of a first passage through the liver. Although nasal administration also has its limits, these limits are widely known and can be easily respected or overcome. In practice, the only limitations that must be considered require mostly that the administered dose of drug should not be too high and that the therapy should not be chronic.

[0007] While in theory all drugs with a systemic effect could be contemplated for nasal administration, in the light of the above considerations, there are nevertheless certain categories of drugs that are more suitable than others for nasal administration. Potential candidates preferred for nasal formulae are analgesic drugs for the treatment of non chronic pain (piroxicam, morphine, dextropropoxyphene, endorphin), tranquillising or sleep-inducing drugs for the treatment of stress pathologies (Diazepam, Lorazepam), antinausea or antiemetic drugs (metoclopramide), antikinosis drugs (dimenidrinat), vitamin B12, calcitonin, nicotine, myorelaxing agents (thiocolchicoside), antimigraine agents, in any case, though without excluding many others.

[0008] As explained above it is of particular importance for the studies concerning the development of inhaling products that the nasal product should be composed of the formula and of the insufflator or dosing device that allows administration of the formula. According to the directives expressed in the Pharmacopoeiae of various countries, the insufflating device and the formula are usually inseparable, in particular in the case of solid formula (powders) and to such an extent that the replacement of the insufflator with another believed similar may (but not necessarily) lead to a variation of bio-availability. This concept is linked to the fact that the nasal absorption of the drug must be preceded by the depositing of the preparation in the nasal cavity. The means of depositing inside the nose depends on the formula, on the insufflator, and in particular on the fluid-dynamic characteristics of the latter, which determine the suspension of the pharmaceutical formula in the flow of conveying gas to produce a cloud of solids. It is clear that, in the absence of a suspension of the formula in the flow of gas, and consequently in the absence of deposition of the formula on the mucosa, there will be no absorption of the substance.

[0009] Anyway, the deposition by insufflation of a drug in the nasal cavity also depends a great deal on its formula. The aerodynamic diameter of the supplied particles is the most important characteristic for the bio-availability of the drug insufflated into the nose. According to a method described in the world's major Pharmacopoeiae (see for example the "Glas Impinger test" (Apparatus A) listed in Farmacopea Europea, III Edition 1997, paragraph 2.9.18., page 143), it has been established that particles with a diameter smaller than 6.4 μm , by insufflation, are certainly deposited in the lungs, whereas those with a larger diameter do not reach the lungs, but are deposited along the airways. Consequently, particles with a diameter smaller than 6.4 micron (μm) are generally classified as "breathable". To ensure deposition in the nose instead of in the lungs, the dimensional distribution of substance supplied is therefore a critical factor.

[0010] Generally, the use of formulae in powder form, rather than liquids, allows a more controlled dimensional interval of the insufflated substance. With respect to a solution, the stability is increased and the bio-availability of the drug could be favoured. After the powder has been deposited on the nasal mucosa it dissolves locally, giving rise to a saturated solution of the drug at the level of the site of absorption, which determines transport through the mucosa at the same rate as the limit flow of the drug. Moreover, to facilitate absorption it is possible to use bioadhesive materials which allow the time of contact of the powder with the mucosa to be extended.

[0011] However, as mentioned above, powders for nasal administration must possess particular dimensional characteristics: they should be fine so that they can be efficiently conveyed by the flow of gas and so that they can be correctly deposited in the nose, but at the same time they should be coarse to facilitate the introduction of the dose in the insufflating device. Moreover, in cases where the insufflator is not loaded with individual pre-established doses of powder, but where an internal mechanism takes the required quantity for each dose one by one from a silo containing the insufflator itself, the powder must also be sufficiently coarse to make dosing efficient and precise at the time of being taken. So, while the powder for producing an aerosol (a cloud of solids dispersed in a flow of gas) must be fine, on the other hand the powder to be dosed in the containers of an insufflator must be fluid, and fluidity is a typical property of coarse powders.

[0012] This paradox is typical of all powders for inhaling, whether they be intended for inhaling through the nose or the lungs. A solution to this paradox, described in patent literature (see for example EP 1 036 562) and applied up till now exclusively for powder for inhaling in the lungs, particularly those with a topical effect, has been the construction of aggregates of particles, held together by weak forces of attraction. These aggregates, called "soft pellets", are prepared from micronised particles having a mean diameter smaller than 10 micron, obtained with a powder grinding (micronising) procedure. Soft pellets have dimensions of a few hundred microns and a roundish shape. For these reasons they are perfectly fluid and suitable for the operations of filling the containers with the dose. Soft pellets are then demolished into the particles making them up through the turbulence in the conveying air flow generated by the aerosol device, substantially restoring the dimensional distribution of the original micronised powder. The fact that the dimensional distribution of the original micronised powder is obtained is critical for the aerosol's ability to be breathed into the lungs, since only particles with an aerodynamic diameter smaller than 6.4 microns can penetrate the lungs. Substantially, as appears in EP 1 036 562, it may be concluded that the objective of the "soft pellets" technology is to make available formulae for pulmonary administration of active principles with a prevalently topical action.

[0013] However, there are some cases, especially when a systemic effect is required, in which nasal administration, if feasible, would be preferable by far to pulmonary administration. In fact there are some drugs which can demonstrate perturbing collateral effects in that they irritate the pulmonary airways and thus produce bronchial spasm, a problem which becomes even more accentuated when patients have to be treated who also suffer from attacks of asthma. Instead, as the nasal mucosae are by nature more exposed to exogenous substances of every type, they are far less sensitive and therefore tend less to become sites of perturbing or even painful conditions for the patient.

[0014] Unfortunately, however, the soft pellets technique is not applicable in the specific field of nasal powders. The main reason is that there is an essential difference between nasal and pulmonary inhalation, consisting of the different required dimension of the particles of product supplied to obtain nasal deposition, in comparison with the pulmonary method. In fact, the dimension of the powder entering the respiratory apparatus to be deposited in the nose must be at

least another of magnitude larger than that intended for the pulmonary route. So for deposition in the nose, the particles must have a diameter at least an order of magnitude larger than 6.4 microns (preferably larger than 10 microns), to avoid their being breathed inadvertently.

[0015] Besides, a technical solution based simply on the preparation of larger particles could compromise the release of the drug, once the powder has been deposited on the nasal mucosa. It is known that the speed of dissolving of a drug in powder form depends on the dimensions of the particles: the smaller the particles, the faster they dissolve. While a decrease of the dissolving speed and also the consequent effect of a delayed and maybe prolonged availability may be acceptable or even desirable in the context of the administration of certain highly soluble drugs with a topical effect, this certainly does not apply to drugs with a topical effect that are not very soluble, and even less in cases where a systemic effect is to be obtained.

[0016] Clearly, for systemic nasal administration carried out to obtain rapid action, it would not be logical to propose the administration of particles with large dimensions, as they would lead to a decrease of the dissolving speed and therefore a slow action. So the particles must absolutely be kept within the range of small dimensions, without at the same time causing them to be breathed into the pulmonary tract. Therefore the paradox of powders for inhalation, in the case of nasal powders, is even more complex, since the particles would have to be small in order to dissolve quickly, but not so fine as to risk being breathed. Moreover they must be sufficiently large to be able to be handled during the preparation and dosing of the pharmaceutical product.

[0017] The aim of the present invention is therefore to overcome the problems described above and therefore to provide formulae of drugs in powder form for nasal, preferably systemic, administration.

[0018] A further aim of the present invention is to provide formulae of drugs in powder form for nasal, preferably systemic, administration which are adaptable to the insufflating devices currently available.

[0019] A further aim of the present invention is to provide procedures for obtaining formulae of drugs in powder form for nasal, preferably systemic, administration.

[0020] A further aim of the present invention is to provide insufflators loaded with formulae of drugs in powder form for nasal, preferably systemic, administration.

[0021] A further aim of the present invention is to provide primary particles that can be used for the formation of agglomerates usable in the formulae of drugs in powder form for nasal, preferably systemic, administration.

SUMMARY

[0022] These and other aims that will appear more clearly below are achieved by the formulae of drugs in powder form as in claim 1. Moreover, claim 22 provides a procedure for obtaining formulae of drugs in powder form as in claim 1. Claims 18 and 21 provide, respectively, a nasal insufflator loaded with a formula as in claim 1 and primary particles for obtaining agglomerates usable in the formulae as in claim 1.

DESCRIPTION OF THE FIGURES

[0023] FIG. 1 shows the primary particles of the pharmaceutical formula and the respective agglomerates according

to the present invention, both reproduced using the technique of scanning electron microscopy ("sem").

[0024] In particular, FIG. 1.A1. shows a photo of the primary particles obtained according to example 1, while FIG. 1.A2. shows the respective agglomerate obtained from those particles, also according to example 1. The length of the white scale marked on each photo corresponds, respectively, to 20 and 200 micron.

[0025] FIG. 1.B1. shows a photo of the primary particles obtained according to example 3, while FIG. 1.B2. shows the respective agglomerate obtained from those particles, also according to example 3. The length of the white scale marked on each photo corresponds, respectively, to 10 and 200 micron.

[0026] FIG. 1.C1. shows a photo of the primary particles obtained according to example 6, while FIG. 1.C2. shows the respective agglomerate obtained from those particles, also according to example 6. The length of the white scale marked on each photo corresponds, respectively, to 20 and 200 micron.

[0027] Instead, FIG. 2 shows the dimensional distribution of the fragments of chimerical agglomerates in example 6 supplied with a Valois insufflator, in comparison with the distribution of the agglomerates before supplying. In particular, on the horizontal axis ("x") of FIG. 2 is shown the diameter of the agglomerates in micron, established by screening, while on the vertical axis ("y") of FIG. 2 is shown the cumulative sub-measure expressed as a percentage. The curve that joins the empty triangles describes the dimensional distribution of the formula according to example 6 before supplying, while the curve that joins the black circles describes the dimensional distribution of the same formula after supplying with a Valois Monopowder P insufflator.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The present patent application aims to provide remedies to the difficulties identified above and therefore describes new preparations in powder form suitable for the nasal administration of drugs, preferably with a systemic effect, by insufflation, insufflating devices loaded with said new preparations, as well as the technique and the intermediate products necessary for their preparation.

[0029] In particular, the preparation of formulae able to overcome the paradox related to the optimum dimensions requires, for nasal application, new technological solutions based on methods and on excipients suitable for the formation of said formulae.

[0030] The present application therefore describes how to make a nasal powder able to satisfy the two different technological requirements for the preparation of the dose and the supply of the prepared substance. Claims are therefore made for nasal formulae made with a new technology with which powders may be obtained which, though composed of primary particles having dimensions of a few micron suitable for rapid dissolving on the mucosa and therefore advantageously suited for systemic administration, are presented as agglomerates of said particles, having dimensions of hundreds of microns, and are therefore suitable for dosing of the drug in the insufflator. The powder for

insufflation described is able to deliver different quantities and numerous types of drugs to the nasal mucosa. 67/01

[0031] To satisfy not only the paradox of inhaling powders in general, but also and above all the paradox of nasal powders in particular, the present patent application describes the construction of agglomerates from primary particles with small dimensions, held together by weak forces of attraction. These agglomerates, on account of their specific behaviour at the time of their suspension in the conveying gas flow to form a cloud of solids dispersed in the gas flow, make up a so-called "chimerical" form of the inhaling powder. They are in fact prepared from primary particles with micronic dimensions (that is from a few μm up to a few tens of μm), in particular having a diameter-volume established by light scattering between 1 and 50 micron, preferably between 1.5 and 29 micron.

[0032] Preferably, the dimensional distribution of the primary particles (in the diameter-volume interval from 1 to 50 micron) is such as to present a median diameter-volume (D_{50}) established by means of light scattering between 3 and 11 micron, 80% of the primary particles falling in the diameter range between 2 micron (D_{10}) and 20 micron (D_{90}), D_{10} constituting the lower diameter percentile value, that is the value not reached by 10% of the population of the primary particles, and D_{90} constituting the higher diameter percentile value, not reached by 90% of the population of primary particles.

[0033] More preferably, the dimensional distribution of the primary particles (in the diameter-volume interval from 1.5 to 29 micron) is such as to present a mean diameter-volume (D_{50}) established by means of light scattering between 4 and 6 micron, 80% of the primary particles falling in the diameter range between 2 micron (D_{10}) and 9 micron (D_{90}), D_{10} constituting the lower diameter percentile value, that is the value not reached by 10% of the population of the primary particles, and D_{90} constituting the higher diameter percentile value, not reached by 90% of the population of primary particles.

[0034] Instead, the agglomerates are composed of primary particles as above and they exist only in the phases that precede the supply of the product. These agglomerates have dimensions of hundreds of microns. In particular, these agglomerates have a diameter of at least 106 micron, selected by screening; more preferably their diameter selected by screening is between 106 and 1000 micron, and their shape is generally spherical or roundish. For these reasons the agglomerates are fluid and suitable for the operations of filling the containers with the dose and for dosing inside the insufflator. The air turbulence produced during insufflation, that is the conveying gas flow supplied, suspending the formula to create a cloud of dispersed solids, demolishes the agglomerates at least partially to create fragments, giving origin—by reduction of the dimensional distribution of the aggregates—to a new powder (composed of agglomerates and their fragments) with a dimensional distribution having a prevaillingly non breathable diameter ($>6.4 \mu\text{m}$), but suitable for nasal deposition.

[0035] In particular, the mist of solids dispersed in the gas flow at the time of supply from the insufflator contains a fraction of at least 80% in weight, preferably of at least 85% in weight, or even more preferably of 90% or even 95% in weight of solids having a non breathable diameter (>6.4

μm). For example, cases are preferred where, in the gaseous suspension composed of agglomerates and their fragments, at least 60% of the weight of the solids has a diameter, selected by screening, larger than 53 micron.

[0036] It should be noted that the reduction of the initial dimensional distribution of the aggregates according to the present invention for disaggregating in the conveying gas flow takes place uniformly but for a relatively small factor (<8), preferably between 1.1 and 3 and even more preferably between 1.1 and 2.

[0037] In particular, according to a preferred form of the present invention, formulae of drugs in powder form are supplied for preferably systemic, nasal administration, by means of a suspension of said powder in a conveying gas flow at the moment of supply from a special insufflator, said powder being composed of agglomerates with a diameter of at least 106 micron selected by screening, composed of homogeneous primary particles comprising the drug and structuring excipients having a diameter-volume established by light scattering between 1 and 50 micron, characterised in that said agglomerates, at the moment of their suspension in the gas flow, are at least partly disaggregated so as to produce, in the cloud of solids dispersed in the gas flow, a fraction of at least 80% in weight, composed of agglomerates and of their fragments, the solids contained in said fraction having a non breathable diameter.

[0038] The present application also describes a procedure for the preparation of a formula of a drug in powder form for nasal administration, which as said above is "chimerical" in that it is presented as composed of agglomerates of small particles (that is "primary" particles), such that once insufflated it is transformed into fragments of such agglomerates, rather than into the original primary particles. The primary particles of this powder, having dimensions of a few micron, in particular between 1 and 50 micron and preferably between 1.5 and 29 micron (diameter-volume established by light scattering) are obtained with a spray drying technique, applied to a solution of auxiliary substances (structuring excipients and possible additional aids) and drug. These particles, having dimensions between 1 and 50 micron, or, preferably between 1.5 and 29 micron, are called primary particles, because after their production they are agglomerated directly to obtain soft agglomerates, with dimensions of a few hundred micron, preferably at least 106 micron, and selected by screening. This procedure, which is described in greater detail below, reduces by one step the method described in patent EP1036562 for pulmonary soft pellets.

[0039] Now, returning to the agglomerates of the present invention, these agglomerates are therefore defined "chimerical agglomerates" because their existence, in terms of dimension, is functional only for the dosing of the powder in the insufflator and limited to the production phases that precede insufflation. After insufflation with an air jet device (or, more generally, with a "conveying gas flow", and therefore independently of the type of gas used to obtain the jet), these chimerical agglomerates are fragmented by the turbulence of the conveying gas flow.

[0040] However, due to the relatively low disaggregating factor (<8, preferably between 1.1 and 3, and more preferably between 1.1 and 2), the fragments obtained are not the primary particles, as described in patent EP 1036562, but still aggregates of the primary particles, though having

dimensions smaller than the chimerical aggregates. In other words, the relatively low disaggregating factor (<8 or preferably between 1.1 and 3, and more preferably between 1.1 and 2) distinguishes the present invention and constitutes a fundamental difference with respect to the "soft pellets" technology, in which one does not seek to obtain a new powder with an intermediate dimension, but one regenerates the primary particles from the agglomerates, obtaining a cloud of particles with a prevalently breathable dimension (<6.4 micron).

[0041] The fragments of chimerical agglomerates of the present invention are particularly suitable for the nasal administration of drugs because, after being deposited on the nasal mucosa, since they are weak aggregates of fine primary particles, they do not prevent a fast dissolving of the drug. At the same time they are prevalently sufficiently coarse to prevent their being breathed.

[0042] While the disaggregating of given chimerical agglomerates of the present invention depends, to a certain extent, also on the fluid-dynamic characteristics of the insufflator used, the experiments carried out by the inventors of the present application have demonstrated that a turbulent conveying gas flow with a speed between 5 l/min and 15 l/min and with a total supplied volume between 5 ml and 80 ml is able to suspend and to disaggregate adequately, according to the present invention, a dose composed of between 0.5 mg and 40 mg of nearly all the samples chosen from a vast range of different formulae (that is comprising different combinations between mean dimensions of primary particles and of aggregates) according to the present invention. While these fluid-dynamic conditions are exemplary only for insufflators by Valois (model Monopowder P), Miat (Miat spa, Milan, Italy) and Puvlizer (Teijin Ltd. Tokyo, Japan), it was found that the disaggregating of the formulae of the present invention was still adequate even in extreme conditions, that is at gas flow rates created artificially with external sources and between 2 l/min and 60 l/min. The possibility of the operation at much slower or much faster flow rates than those prescribed further confirms the versatility of nasal powders according to the present invention. In particular, in the case of slow supply (for example with the Puvlizer insufflator), despite the need for several activations until the complete dose has been supplied, no substantial impact was found on the dimensional distribution of the supplied cloud of solids which always fell within the criteria of the present invention. Moreover, the experiments have demonstrated that even a gas flow rate much higher than the one usually generated in the insufflators currently on the market does not regenerate the primary particles, but maintains the dimensional distribution of the supplied cloud of solids within the range contemplated by the present invention. Consequently, it has been demonstrated that the formulae of drugs in powder form according to the present invention are suitable for use with all the nasal insufflators currently on the market (or are easily adaptable by the expert in the field, by selecting a suited combination of the size of the primary particles and of their agglomerates).

[0043] It has thus been seen how the new technology described in the present application is able to control the dimension of an agglomerate of primary particles during supply and guarantees that an aerosol will be obtained that is suitable for depositing the drug at the level of the nasal mucosa after insufflation in the nostrils. In this way the

possibility of the supplied material entering the lungs is very slight. The peculiar formula of the primary particles and the method adopted for preparing them ensure that these primary particles give rise to agglomerates which, when subjected to a turbulent jet of conveying gas, produce fragments larger than the primary particles. Moreover, these "chimerical" agglomerates and their fragments, on account of their composition, in the presence of water or of mucous are instantly decomposed or disaggregated into the primary particles, without in this way limiting the dissolving of the drug carried. Thus, the availability for rapid absorption through the nasal mucosa—which is critical, for example, for a formula with a systemic effect, but may also be contemplated for determined topical applications, when the active principle presents very poor solubility—is therefore not prevented by the agglomeration.

[0044] In particular, the primary particles according to the present invention are prepared by means of a spray drying method of a solution comprising the drug and one or more structuring excipients, together with optional adjuvant excipients, for example through the drying of an aqueous or water-alcohol solution of a drug and excipients. The structuring excipients are described in more detail below. Among adjuvant excipients, the leading ones to be mentioned are surface-active substances. Further adjuvant excipients may be chosen and incorporated in suitable quantity where necessary—by the expert in this field, from the "usual" excipients in this field, that is from those authorised by the Pharmacopeia. A non limiting example for a class of further adjuvant excipients is represented by the various pharmaceutically acceptable preserving agents.

[0045] The method according to the present invention allows primary particles to be obtained directly in the desired dimensional interval, avoiding subsequent grinding operations.

[0046] The structuring excipients necessary for the formation and for the structuring of the primary particles may be used individually or as blends and they are chosen from the group that consists of sugars, amino acids, cellulose polymers, cyclodextrines, chitosane, solid polyethylenglycols and polyalcohols.

[0047] In particular, among the polyalcohols, mannitol, sorbitol and xylitol are to be mentioned.

[0048] In particular, among the sugars, lactose, sucrose, glucose, trehalose and fructose are to be mentioned.

[0049] In particular, among the amino acids, glycine, leucine and isoleucine are to be mentioned.

[0050] In particular, among the semi-synthetic cellulose polymers the natural or semi-synthetic celluloses are to be mentioned, for example methylcellulose or hydroxypropylmethylcellulose.

[0051] The primary particles (and also the agglomerates subsequently obtained from them) are characterised in that the active principle (that is the drugs) contained in them replaces the structuring excipient (or the blend of structuring excipients) in a percentage between 0.1 and 90% and that these drugs are for example chosen from the group that comprises analgesics; anti-cough drugs; tranquillisers; sleep-inducing drugs; drugs used in the therapy to break the habit of smoking alcohol and opioids.

[0052] antidepressants; antinausea; antiemetics; antihistamines; anticoagulants; antikinetic drugs; myorelaxing agents; antispastic agents; antimigraine agents; drugs for the treatment of neurodegenerative diseases, of erectile dysfunctions, of osteoporosis, of sterility; antineoplastic agents; local anaesthetics; antianaemic agents; hypoglycaemic agents; peptides; vaccines; vitamins; hormones and antistress agents.

[0053] Preferably the drugs are chosen from the group that comprises piroxicam, dextropropoxyphene, endorphin, diazepam, dimenidrinat, thiocolchicoside, almitidan, apomorphine, buprenorphine, bupropion, buserelin, butorphanol, calcitonin, codeine, desmopressin, dihydroergothamin, L-dopa, doxepin, enalaprilate, dronabinol, recombinant human erythropoietin, folic acid, G-CSF (Granulocyte Colony Stimulating Factor), growth hormone secretagogues (GHRP-6), glucagon, gonadorelin, goserelin, aloperidol, heparin, hydromorphon, growth hormone, insulin, LHRH, lorazepam, lidocain, lipressin, melatonin, meperidin, methyphenidate, metoclopramide, midazolam, morphine, nafarelin, nalbupin, naltrexone, nicotine, estradiol, oxytocin, progesterone, prometazin, propranolol, parathyroid hormone, raloxifene, serotonin, sildenafil, tamoxifene, testosterone, tetracosactide, derivatives of delta-9-tetrahydrocannabinol, sumatriptan, urokinase, vitamin B12, endorphins, thiocolchicosides and caffeine.

[0054] Depending on the composition and on the presence of the structuring excipients as above, these primary particles may be grouped together to form chimerical agglomerates. The primary particles are agglomerated by making them roll in a cylindrical or kidney-shaped glass container which rotates on its own base. The inventors of the present application have found, however, that, if the rolling container is made of bakelite, the formation of the agglomerates is faster, more reproducible and quantitative, even starting from powders that do not tend to form electrostatic charges.

[0055] In particular, the procedure preferred for obtaining formulae of drugs in powder form according to the present invention comprises the following phases:

[0056] the preparation of a solution comprising the drug and the structuring excipients and optional adjuvant excipients, for example surface-active substances,

[0057] spray drying to give the primary particles

[0058] agglomeration of the primary particles by rolling,

[0059] selection of the agglomerates with a diameter of at least 106 micron,

[0060] In cases where the drug and the structuring excipient (or one of the optional adjuvant excipients, in particular surface-active substances) are not soluble in the same solvent, the solution comprising the drug and the structuring excipient or the structuring excipients and the optional adjuvant excipients, in particular surface-active substances, is obtained by mixing a first solution of the drug with one or more second solutions of structuring excipients and optionally of adjuvant excipients, in particular surface-active substances. Preferably, mixing is carried out in such proportions as not to cause precipitations of the solutes. Preferably, to obtain the different solutions solvents are used which are

without the risk of being breathed. This objective is achieved by the formula according to the present invention, since the dimensional distribution of the nasal powder is such that at least 80% of the weight of the cloud of solids supplied by the insufflator has a non breathable diameter, that is larger than 6.4 micron. The demolition of the chimerical agglomerates according to the present invention therefore leads to the obtaining of fragments which are still composed of aggregates of primary particles, and which as such possess dimensions of some tens or hundreds of micron.

[0123] The powder of chimerical agglomerates obtained according to example 6, emitted by the Valois insufflator, was therefore collected from a series of screens, in order to determine the dimensional distribution of the cloud of powder supplied. The result of this measurement is shown in FIG. 2, in comparison with the original dimension of the agglomerates. It may be seen that the emission of the powder (having a mean dimension of about 400 micron) has provoked the breaking up (for a factor of about 2) of the agglomerates into fragments having a mean dimension of about 200 micron, particularly suitable for nasal deposition, since they are still composed of aggregates of primary particles. Moreover, it may be seen from FIG. 2 that about 84% of the fragments produced have a diameter larger than 75 micron. Moreover, to measure the fraction of fine (breathable) particles in the cloud of solids emitted by the Valois (Monopowder P) insufflator, the formulae according to examples 1-6 were subjected to the "Glas Impinger test (Apparatus A)" as listed in the European Pharmacopeia, edition III 1997, paragraph 2.9.18., page 143. The values of fractions of breathable particles (<6.4 micron) measured on the different formulae according to the examples 1-6 were in all cases less than 5% of the weight.

[0124] Determination of the Dissolving Speed of Caffeine by the Chimerical Agglomerates

[0125] The presence in the supplied products of fragments of some hundreds of micron is desirable to ensure deposition in the nose, but at the same time it must not limit the dissolving of caffeine by the primary particles. To check this, 50 mg of chimerical agglomerates obtained according to example 6 were put into a container of distilled water at 37° C., kept constantly agitating. At set intervals of time, an amount of solution was analysed to determine the quantity of dissolved caffeine. The result obtained showed that the whole dose of powder was dissolved in less than one minute.

1-28. (canceled)

29. Method for obtaining drug formulae in powder form comprising the following phases:

the preparation of a solution comprising a drug and one or more structuring excipients and optional adjuvant excipients, for example surface-active substances,

spray drying to give homogeneous primary particles having a diameter-volume established by light-scattering comprised between 1 and 50 micron,

agglomeration of the primary particles by rolling,

selection of the agglomerates with a diameter of between 106 and 1000 micron.

30. Method according to claim 29, wherein the solution comprising the drug and the structuring excipient or the structuring excipients and the optional surface-active sub-

stances is obtained by mixing a first solution of the drug with one or more second solutions of structuring excipients and of optional adjuvant excipients, in particular surface-active substances.

31. Method according to claim 29, wherein the first solution and the second solution or the second solutions are obtained using different solvents which can be mixed with each other.

32. Method according to claim 31, wherein the first solution and the second solution or the second solutions are obtained using different solvents with the addition of a further (co-) solvent as a miscibility mediator.

33. Method according to claim 29, wherein the drugs replace the structuring excipient in a in a percentage between 0.1 and 90% by weight and are chosen from the group that comprises analgesics; anti-cough drugs; tranquilisers; sleep-inducing drugs, drugs used in the therapy to break the habit of smoking, alcohol and opioids; antidepressants; antinausea; antiemetics; antihistamines; anticoagulants; antikinetic drugs; myorelaxing agents; antispastic agents; antimigraine agents; drugs for the treatment of neurodegenerative diseases, of erectile dysfunctions, of osteoporosis, of sterility; antineoplastic agents; local anaesthetics; antianaemic agents; hypoglycaemic agents; peptides; vaccines; vitamins; hormones and antistress agents.

34. Method according to claim 33, wherein the drugs are chosen from the group that comprises piroxicam, dextro-propoxyphene, endorphin, diazepam, dimenidrinat, thio-colchicoside, almitidan, apomorphine, buprenorphine, bupropion, busarelin, butorphanol, calcitonin, codeine, desmopressin, dihydroergothamin, L-dopa, doxepin, enalaprilate, dronabinol, recombinant human erythropoietin, folic acid, G-CSF (Granulocyte Colony Stimulating Factor), growth hormone secretagogues (GHRP-6), glucagon, gonadorelin, goserelin, aloperidol, heparin, hydromorphon, growth hormone, insulin, LHRH, lorazepam, lidocain, lipressin, melatonin, meperidin, methylphenidate, metoclopramide, midazolam, morphine, nafarelin, nalbuphin, naltrexone, nicotine, estradiol, oxytocin, progesterone, prometazin, propranolol, parathyroid hormone, raloxifene, serotonin, sildenafil, tamoxifene, testosterone, tetracosactide, derivatives of delta-9-tetrahydrocannabinol, sumatriptan, urokinase, vitamin B12, endorphins, thio-colchicosides and caffeine.

35. Method according to claim 29, wherein the structuring excipients are chosen from one or more substances chosen from the group that consists of polyalcohol, sugars, amino acids, cellulose polymers, cyclodextrines, chitosane and solid polyethylenglycols.

36. Method according to claim 35, wherein the polyalcohols are chosen from the group that consists of mannitol, sorbitol and xylitol.

37. Method according to claim 35, wherein the sugars are chosen from the group that consists of lactose, sucrose, glucose, trealose and fructose.

38. Method according to claim 35, wherein the amino acids are chosen from the group that consists of glycine, leucine and isoleucine.

39. Method according to claim 35, wherein the cellulose polymers comprise natural or semi-synthetic celluloses, for example methylcellulose or hydroxypropylmethylcellulose.

40. Method according to claim 29, wherein the primary particles also comprise one or more adjuvant excipients, for example surface-active substances.

41. Method according to claim 40, wherein the adjuvant excipients, for example surface-active substances, are present in a percentage of weight, with reference to the quantity of the total dry formula, between 0.1% and 10% and are chosen from the group that consists of phospholipids, for example lecithin, semi-synthetic mono- or diglycerides, sorbitan esters, polyoxyethylsorbitan esters and poloxamers.

42. Method according to claim 29, wherein spray drying is carried out with a Mini Spray Dryer Buechi Model B-191 device in the following operative conditions:

input air temperature: 90° C.;

output air temperature: 38-40° C.;

solution flow rate: 6.5 ml/min;

nozzle diameter: 1.0 mm;

air flow rate: 600 l/h.

43. Method according to claim 29, wherein rolling for agglomeration of the primary particles is carried out in a cylindrical or kidney-shaped bakelite or glass container which rotates on its own base.

44. Method according to claim 29, wherein the selection of the agglomerates is carried out by screening.

45. Homogeneous primary particles having a diameter-volume established by light scattering comprised between 1 and 50 micron obtainable by spray drying of a drug solution

containing also one or more structuring excipients and adjuvant excipients, in particular surface-active substances.

46. Drug formulae in powder form for nasal administration, said powder being composed of agglomerates with a diameter of between 106 and 1000 micron selected by screening, composed of homogeneous primary particles comprising the drug and structuring excipients having a diameter-volume established by light scattering comprised between 1 and 50 micron, and wherein said agglomerates are obtainable by the process of claim 29.

47. Drug formulae in powder form according to claim 46, wherein homogeneous primary particles comprising the drug and structuring excipients have a diameter-volume established by light scattering between 1.5 and 29 micron.

48. Nasal insufflator, filled with a drug formula according to claim 46.

49. Nasal insufflator according to claim 48, able to generate a conveying gas flow having a speed between 5 l/min and 15 l/min for the suspension of the drug-formulae in powder form and to give a cloud of solids dispersed in the gas flow.

50. Nasal insufflator according to claim 49, chosen from the group that consists of the Puvlizer, Mist and Valois insufflator.

* * * * *

101 99

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
EMILIO FERRERO

ASUNTO

Radicación 07-79189
Trámite 011
Evento 378
Actuación 411
Oficio
Folios 0018

202776

Patente de Invención

☒

Patente de Modelo de Utilidad

☐

Vía Nacional

☐

Vía PCT (fase nacional)

☒

Cap. I

☒

Cap. II

☐

No. Sol. Internacional

PCT/EP2006/050215

Fecha de Presentación Interna.

16/01/2006

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:

1. Documentos estudiados

Descripción: Folios 38-52 como se radicó inicialmente
Reivindicaciones: Folios 53-61 como se radicó inicialmente
Prioridad: Folio 1 DE, 102005005505.2, 04-02-2005
DE, 102005036216.8, 02-08-2005

2. Objeto de la invención

Título de la solicitud: USO DE INHIBIDORES DE TIROSINA QUINASA PARA EL TRATAMIENTO DE RINOSINOSITIS CRONICA (folio 1).

El problema técnico planteado en esta solicitud está relacionado con la necesidad de usar compuestos inhibidores de EGFR quinasa, especialmente quinazolinás, quinolinás y pirimido-pirimidinas en la preparación de medicamentos para el tratamiento de pólipos nasales, rinosinusitis, en especial rinosinusitis crónica (folios 38 y 45; pág. 1 y 8).

Para solucionar este problema técnico la solicitud en estudio proporciona el uso de un compuesto *-derivados de quinazolina, pirrolo-pirimidina, pirimido-pirimidina o quinolina-* seleccionado de un grupo dado de una lista de 201 compuestos (reivindicaciones 1-9); medicamentos en forma de polvo, en forma suspensión o disolución para aplicación nasal que contienen un compuesto de la reivindicación 1; y un método de tratamiento.

102/100

El objeto de la presente solicitud se cataloga en A61K31/517, A61P11/00, de acuerdo con la Clasificación Internacional de Patentes (IPC).

3. De la solicitud de Patente

3.1 Reivindicaciones (artículo 30 D 486)

Existe falta de claridad y concisión en las reivindicaciones independientes 10-12 por la expresión "al menos uno de los compuestos mencionados en la reivindicaciones 1 ó 2"; es necesario que la expresión "al menos uno" sea eliminada o cambiada por un término concreto acorde con la materia soportada.

4. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

De acuerdo con los artículos anteriores, las reivindicaciones 1-9 que reclaman el uso de un compuesto no son patentables puesto que el uso no es un producto o un procedimiento tecnológico; por tanto, tales reivindicaciones deben eliminarse del alcance de la solicitud.

5. Excepción a la patentabilidad (artículo 20 D486 literal d)

De acuerdo con el artículo anterior, las reivindicaciones 13-17 que se relacionan con un método de tratamiento están exceptuadas de patentabilidad; por ende, dichas reivindicaciones deben eliminarse del alcance de la solicitud.

6. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente es 04-02-2005 se buscaron documentos del estado de la técnica relacionados.

Nº	Documento	Título	Fecha Publicación
D1	US20030149062	Use of tyrosine kinase inhibitors for the treatment of inflammatory processes	07-08-2003
D2	US20050019411	Powder for nasal administration of drugs.	27-01-2005

D1 en folios 87-92 y D2 en folios 93-100.

D1 se relaciona con un método para tratar enfermedades inflamatorias de las vías respiratorias o de intestino, que consiste en administrar derivados de quinazolina de formula (I) u otros inhibidores de tirosina quinasa (folio 87, portada).

D2 se relaciona con formulaciones de un fármaco en forma de polvo para administración nasal y un método para hacer dichas formulaciones disponibles, así como a las partículas primarias para obtener aglomerados de (folio 93, portada).

7. Análisis de patentabilidad (artículo 14 D486)

7.1. Novedad (artículo 16 D486)

Se solicita en las reivindicaciones 11-12 medicamentos en forma de suspensión y en forma de una disolución para la aplicación nasal que contienen un compuesto de la reivindicación 1 (*derivados de quinazolina, pirrolo-pirimidina, pirimido-pirimidina o quinolina*) con uno o varios excipientes.

SOLICITUD	D1
Medicamentos para inhalación en forma de suspensión y en forma de solución que contiene:	SI Medicamentos para inhalación en forma de suspensión y en forma de solución que contiene:
un compuesto de la reivindicación 1 (<i>derivados de quinazolina, pirrolo-pirimidina, pirimido-pirimidina o quinolina</i>)	SI un compuesto derivados de quinazolina, pirrolo-pirimidina, pirimido-pirimidina o quinolina (folios 91-92; pág. 17-18)
con uno o varios excipientes	SI con uno o mas excipientes farmacéuticamente aceptables (folios 89-90; pág. 7-8)

Dado que en D1 ya se divulgan medicamentos para inhalación en forma de suspensión y en forma de solución, que contienen compuestos derivados de quinazolina, pirrolo-pirimidina, pirimido-pirimidina y quinolina (*compuestos iguales a los señalados en la reivindicación 1 de la solicitud*) con uno o mas excipientes o vehículos convencionales; se considera que la materia reclamada no cumple el requisito de novedad.

7.2. Nivel inventivo (artículo 18 D486)

Se solicita en la reivindicación 10 un medicamento en forma de polvo para la aplicación nasal que contiene un compuesto de la reivindicación 1 (*derivado de quinazolina, pirrolo-pirimidina, pirimido-pirimidina o quinolina*) con un tamaño de partícula promedio entre 0,1 a 200 µm y opcionalmente uno o mas excipientes.

SOLICITUD	D1	D2
Medicamentos para inhalación en forma de suspensión y en forma de solución que contiene:	SI Medicamentos para inhalación en forma de suspensión y en forma de solución (folio 90; pág. 8) que contiene:	SI Medicamentos para inhalación en forma de polvo que contiene: (folios 96; pág. 3)
un compuesto de la reivindicación 1 (<i>derivados de quinazolina, pirrolo-pirimidina, pirimido-pirimidina o quinolina</i>)	SI un compuesto derivados de quinazolina, pirrolo-pirimidina, pirimido-pirimidina o quinolina (folios 91-92; pág. 17-18)	NO un fármaco (folios 96; pág. 3)
con tamaño de partícula entre (0,1-200) µm	NO	SI con tamaño de partícula entre (0,1-200) µm (folios 97; pág. 4, párrafo 0038).
con uno o varios excipientes	SI con uno o mas excipientes farmacéuticamente aceptables (folios 89-90; pág. 7-8)	SI con uno o mas excipientes farmacéuticamente aceptables (folios 98; pág. 5)

En el estado de la técnica se encuentra D1 que divulga medicamentos para inhalación en forma de polvo que contienen compuestos derivados de quinazolina, pirrolo-pirimidina, pirimido-pirimidina y quinolina con uno o mas excipientes o vehículos fisiológicamente aceptables, tal como se muestra en la tabla comparativa.

Así, la solicitud se diferencia de D1 en que señala que el fármaco tiene un tamaño de partícula promedio entre 0,1 a 200 μm .

Y el efecto técnico que logra tal diferencia es obtener un medicamento en forma de polvo con tamaño adecuado del fármaco para la aplicación nasal.

De manera tal, que el problema técnico objetivo de la solicitud está relacionado con la necesidad de obtener un medicamento en forma de polvo con tamaño adecuado del fármaco para la aplicación nasal.

No obstante, se encuentra que D2 enseña que en la preparación de formulaciones para administración nasal las partículas primarias del fármaco están entre 1 a 50 μm (folios 97; pág. 4, párrafo 0038).

Asimismo, se encuentra que la solicitud señala que el tamaño de partícula promedio del fármaco está en el rango preferido entre 5 a 25 μm (folio 48; pág. 11).

Por consiguiente, para un experto en la materia el medicamento reclamado es obvio a las enseñanzas de D1 y D2, por lo que esta materia no tiene nivel inventivo.

8. Conclusión

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 artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
18 FEB. 2011

CONCEPTO TECNICO No. 237	EXAMINADOR TECNICO Código No. 202079
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