(12) STANDARD PATENT (11) Application No. **AU 2006224619 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Taste masked dosage form containing roflumilast

(51) International Patent Classification(s)
A61K 9/16 (2006.01) ***A61P 11/06*** (2006.01)
A61K 31/166 (2006.01)

(21) Application No: **2006224619** (22) Date of Filing: **2006.03.14**

(87) WIPO No: **WO06/097456**

(30) Priority Data

(31) Number	(32) Date	(33) Country
05102058.4	**2005.03.16**	**EP**

(43) Publication Date: **2006.09.21**
(44) Accepted Journal Date: **2012.06.07**

(71) Applicant(s)
Nycomed GmbH

(72) Inventor(s)
Pontius, Alexander;Brueck-Scheffler, Antje

(74) Agent / Attorney
Griffith Hack, GPO Box 1285, Melbourne, VIC, 3001

(56) Related Art
US 2004/058896 A1
US 2006/0198889 A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 September 2006 (21.09.2006)

PCT

(10) International Publication Number
WO 2006/097456 A1

(51) International Patent Classification:
A61K 9/16 (2006.01) *A61P 11/06* (2006.01)
A61K 31/166 (2006.01)

(21) International Application Number:
PCT/EP2006/060679

(22) International Filing Date: 14 March 2006 (14.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
05102058.4 16 March 2005 (16.03.2005) EP

(71) Applicant *(for all designated States except US)*: **ALTANA PHARMA AG** [DE/DE]; Byk-gulden-str. 2, 78467 Konstanz (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BRÜCK-SCHEFFLER, Antje** [DE/DE]; Clara-schumann-str. 5, 78464 Konstanz (DE). **PONTIUS, Alexander** [DE/DE]; Fichtenweg 5, 66822 Lebach (DE).

(74) Agents: **KRATZER, Bernd** et al.; C/o Altana Pharma AG, P.o. Box 100310, 78403 Konstanz (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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

(54) Title: TASTE MASKED DOSAGE FORM CONTAINING ROFLUMILAST

(57) Abstract: Taste masked dosage forms for oral administration of roflumilast are described.

WO 2006/097456 A1

TASTE MASKED DOSAGE FORM CONTAINING ROFLUMILAST

Technical field

The present invention relates to the field of pharmaceutical technology and describes taste masked particles and dosage forms for oral administration of roflumilast as active ingredient for treating diseases such as asthma or airway obstructions. The invention additionally relates to processes for producing the particles and dosage form.

Prior art

Cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4) are currently of special interest as a new generation of active ingredients for treating inflammatory disorders, especially inflammations of the airways such as asthma or airway obstructions (such as, for example, COPD = chronic obstructive pulmonary disease). A number of PDE 4 inhibitors is currently undergoing advanced clinical testing inter alia the PDE 4 inhibitor N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (INN: roflumilast).

WO 03/070279 is related to a dosage form for oral administration of a PDE 4 inhibitor whose solubility is slight, which contain PVP as a binder. Inter alia the PDE 4 inhibitor N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (INN: roflumilast) is mentioned in connection with the dosage form.

For pediatric or geriatric patients who cannot swallow a tablet, alternate administration forms such as a liquid suspension, oral granule formulation or orodispersible administration forms would be desirable to administer roflumilast. However roflumilast is observed to present an unpleasant taste respectively a numbness sensation, when exposed in the oral cavity. Overcoming unpleasant or bad taste of certain pharmaceutical active ingredients (drugs) is a continuous challenge for formulation scientist. A commonly used method to mask the taste of badly tasting drug substances and medications is the coating by a polymeric film, thereby avoiding the contact of the pharmaceutical active ingredient with the tongue and the oral cavity. Such coating can e.g. be performed on tablets, pellets, granulates and drug crystals. A commonly applied method to perform such a coating is in conventional pans (mainly for tablets) or in a fluidized bed process. In order to assure a proper coating in the fluidized bed, the coating process is typically performed by employing a so-called Wurster tube. In case of drug containing pellets, a multi-stage manufacturing process is necessary. Drug containing pellets can either be prepared by an extrusion process or by layering a drug substance on starter pellet cores made out of, e.g. cellulose or saccharose. For the latter method a solution or suspension of the drug

substance is sprayed upon the starter pellets. In a second process step the coating layer is applied for taste masking. This is normally also done in a fluidized bed process by employing a Wurster tube. In the same way as pellets are coated, drug crystals, tablets or granulates can be coated.

WO 2005/013944 is related to a flavoured and taste-masked pharmaceutical composition comprising a plurality of pharmaceutically acceptable cores, such as microspheres, said pharmaceutically acceptable cores comprising etoricoxib, wherein the pharmaceutically acceptable cores are coated with a flavored taste-masking coating solution in a one-step coating process. However the process as described in WO 2005/013944 requires the provision of etoricoxib containing cores in a first step, which are then coated in a one-step coating process with a taste-masking coating solution or dispersion.

WO 02/45693 is related to new preparations for an active ingredient, which is present essentially uniformly dispersed in an excipient matrix composed of one or more excipients selected from the group of fatty alcohol, triglyceride, partial glyceride and fatty acid ester. In the case of active ingredients, which have an unpleasant taste or, for example, show a local anesthetic effect in the mouth after administration, it has been observed that an unpleasant taste of the active ingredient can be masked, and anesthetic effects in the mouth can be avoided, by preparations of the invention. Roflumilast is mentioned as active ingredient in examples 17 to 24 and 33.

The present invention generally relates to providing a taste masked pharmaceutical composition comprising roflumilast, which provides an effective taste masking and which can be prepared avoiding multi-stage manufacturing processes.

Summary of the Invention

The present invention generally relates to coated particles comprising a suitable carrier and a coating layer surrounding the carrier, which coating layer comprises a suitable coating polymer selected from the group of polyvinylpyrrolidone (PVP), cellulosic polymers, acrylic polymers, methacrylic copolymers, starch polymer, chitosan or mixtures thereof, optionally further pharmaceutically acceptable excipients and an active ingredient selected from the group of roflumilast, pharmaceutically acceptable salt of roflumilast, solvate or physiologically functional derivative thereof and mixtures thereof.

The present invention provides coated particles comprising a suitable carrier and a coating layer surrounding the carrier, which coating layer comprises a suitable coating polymer selected from the group of polyvinylpyrrolidone (PVP), cellulosic polymers, acrylic polymers, methacrylic

copolymers, starch polymer, chitosan or mixtures thereof, optionally further pharmaceutically acceptable excipients and an active ingredient selected from the group of roflumilast, pharmaceutically acceptable salt of roflumilast, solvate or physiologically functional derivative thereof and mixtures thereof, wherein the coated particle has a mean particle size less than or equal to 2 mm.

The present invention also provides a coated particle as described above, additionally containing an outer overcoating.

The present invention further provides a process for producing a coated particle as described above, comprising the following steps:

(a) providing a suspension or solution of the active ingredient in a coating polymer solution or dispersion, optionally containing other suitable pharmaceutically acceptable excipients; and

(b) spraying the solution or dispersion of step (a) on the carrier; and

(c) optionally spraying a polymer solution or dispersion on the coated particles of step (b).

The present invention also further provides a dosage form comprising a therapeutically effective amount of an active ingredient selected from the group of roflumilast, pharmaceutically acceptable salt of roflumilast, solvate or physiologically functional derivative thereof and mixtures thereof in the form of coated particles as described above together with one or more pharmaceutically acceptable excipients.

The present invention also further provides a method for the treatment or prophylaxis of a disease regarded as treatable or preventable by PDE 4 inhibitors, wherein a dosage form as described above is administered.

The present invention also further provides use of the coated particles as described above in the manufacture of a medicament for the treatment or prophylaxis of a disease regarded as treatable or preventable by PDE 4 inhibitors.

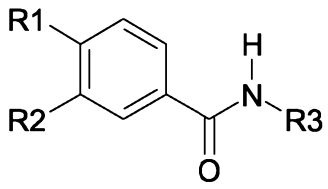
Description of the invention

Surprisingly it has been found that the unpleasant taste of roflumilast can be effectively masked by providing roflumilast in a pharmaceutical dosage form based on coated particles comprising a suitable carrier and a coating layer surrounding the carrier, which coating layer comprises a suitable coating polymer, roflumilast and optionally further pharmaceutically acceptable excipients. The coated particles according to the invention advantageously can be prepared in a one-step process.

2006224619 11 May 2012

The present invention therefore relates to coated particles comprising a suitable carrier and a coating layer surrounding the carrier, which coating layer comprises a suitable coating polymer, optionally further pharmaceutically acceptable excipients and an active ingredient selected from the group of roflumilast, pharmaceutically acceptable salt of roflumilast, solvate or physiologically functional derivative thereof and mixtures thereof.

Roflumilast is the INN for a compound of the formula I



(I)

in which

R1 is difluoromethoxy,

R2 is cyclopropylmethoxy and

R3 is 3,5-dichloropyrid-4-yl.

This compound has the chemical name N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (INN: roflumilast). By the term "physiologically functional derivative" is meant a chemical derivative of roflumilast having the same physiological function as roflumilast, for example, by being convertible in the body thereto or by being an active metabolite of roflumilast. Physiological functional derivatives of roflumilast, which may be mentioned in connection with the invention are for example the N-oxide of roflumilast, and its salts and solvates. The N-oxide of roflumilast has the chemical name 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl-1-oxide)benzamide. The compound of the formula I, its salts, the N-oxide, its salts and the use of these compounds as phosphodiesterase (PDE) 4 inhibitors are described in the international patent application WO 95/01338.

Roflumilast, pharmaceutically acceptable salt of roflumilast, solvate or physiologically functional derivative thereof and mixtures thereof is hereinafter also referred to as active ingredient.

Salts suitable for compounds of the formula I - depending on the substitution - are all acid addition salts but, in particular, all salts with bases. Particular mention may be made of the pharmacologically acceptable salts of the inorganic and organic acids and bases normally used in pharmaceutical technology. Pharmacologically unacceptable salts, which, for example, may be the initial products of the process for preparing the compounds of the invention on the industrial scale are converted into pharmacologically acceptable salts by processes known to the skilled worker. Those suitable on the one hand are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid, or 3-hydroxy-2-naphthoic acid, the acids

being employed to prepare the salts in the equimolar ratio of amounts, or one differing therefrom - depending on whether the acid is monobasic or polybasic and depending on which salt is desired.

On the other hand, salts with bases are also particularly suitable. Examples of basic salts which may be mentioned are lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, once again the bases being employed to prepare the salts in the equimolar ratio of amounts or one differing therefrom.

The coated particles according to the invention preferably have a mean particle size less than or equal to 2 mm and preferably equal to or less than 1 mm. It is particularly preferred to have a mean particle size less than or equal to 400 µm as coated particles of this size will provide a good mouthfeel in the oral cavitiy of a patient. By providing such a small particle size grittiness and a sandy mouthfeel can be avoided. In a preferred embodiment the coated particles according to the invention have a mean particle size in the range from 100 to 400 µm.

The coated particle according to the invention comprises a suitable carrier, which is surrounded by a coating layer. Suitable carriers according to the invention, which may be mentioned, are preferably based on inert excipients, which are customarly used in formulation technology as carriers. Excipients, which may preferably be mentioned, are selected from the group of mannitol, saccharose, lactose (e.g. lactose monohydrate), glucose, erythritol, xylitol, cellulose, microcrystalline cellulose, starch, croscarmellose sodium, crospovidone and mixtures thereof. Carriers according to the invention may be based on powders, granules, small beads, particles, pellets, starter pellets, nonpareils of suitable size composed of the above excipients or mixtures thereof. If a defined shape (e.g. a round shape) of the coated particles is desired it is advantageous to use carriers of a defined shape and size such as starter pellets made of microcrystalline cellulose or saccharose (nonpareilles). Carriers may also be obtained by (pre)granulation of the above excipients to provide carriers with a suitable size.

In one embodiment according to the invention the carrier is composed of microcrystalline cellulose, lactose monohydrate and croscarmellose sodium.

Carriers based on powders, granules, small beads, particles or pellets preferably have a mean particle size less than or equal to 2 mm and preferably equal to or less than 1 mm. It is particularly preferred to have a particle size less than or equal to 400 µm. In a preferred embodiment the carrier according to the invention has a suitable particle size, which after being layered with a coating layer results in coated particles which have a mean particle size in the range from 100 to 400 µm.

Suitable polymers for forming the coating layer surrounding the carrier in the particles according to the

invention can be composed of water-soluble or water-insoluble coating polymers or mixtures thereof. Polymers which may be mentioned in connection with the invention are for example selected from the group of polyvinylpyrrolidon (PVP), cellulosic polymers such as ethylcellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropyl cellulose (HPC), cellulose acetate phthalate, hydroxypropylmethylcellulosephthalate, acrylic polymers such as acrylate ammoniomethacrylate copolymer (Eudragit® RL100 or RS100 or Eudragit® RL30D or RS30D), ethylacrylate methylmethacrylate copolymer (Eudragit ® NE30D), or methacrylic copolymers (Eudragit® L100-55 or Eudragit ® L30D, Eudragit ® E100, Eudragit ® E PO), starch polymer, chitosan, and mixtures thereof.

In a preferred embodiment the coating polymer is selected from the group of water-soluble polymers, preferably selected from the group of starch polymer, hydroxypropylmethylcellulose (HPMC), , hydroxypropyl cellulose (HPC), polyvinylpyrrolidon, chitosan, methacrylic copolymers (Eudragit® L100 or Eudragit ® L100-55 or Eudragit ® L30D-55, Eudragit ® E100, Eudragit ® E PO) and mixtures thereof. Polymers which show a pH dependent water solubility are particularly preferred. Eudragit ® E PO (basic butylated methacrylate copolymer, Ph. Eur.) which is a copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters, also referenced as poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1 is particularly preferred (see Product specification Röhm, Pharma polymers and Handbook of Pharmaceutical Excipients, fourth edition, American Pharmaceutical Association). This polymer is swellable and permeable above pH 5 and soluble below pH 5. Due to these characteristics this polymer provides taste-masking in the mouth and release of roflumilast under acidic conditions in the stomach.

Depending on the polymer used, the active ingredient is either present in the coating layer in suspended form or dissolved, preferably homogeneously suspended or homogeneously dissolved. In the case of the active ingredient being present in suspended form, the active ingredient is present in the form of particles with a mean particle size in the range from 0.1-100 µm. Particles of the active ingredient having a mean particle size in the range from 1 to 10 µm can for example be obtained by micronization (milling by air jet) of the active ingredient of greater particle size or by a suitable crystallization process.

According to the invention the active ingredient is preferably embedded within the polymer of the coating layer surrounding the carrier. It is the embedding of the active ingredient within the coating layer, which provides the taste-masking. It is therefore not necessary to have a coating layer completely or continuously surrounding the carrier. Coated particles comprising a suitable carrier and a coating layer surrounding the carrier according to this invention do not necessarily need a continuous or complete coating layer to obtain a taste-masking.
Optionally further pharmaceutically acceptable excipients can be present in the coating layer of the coated particle according to the invention. Excipients, which may be mentioned in this connection are selected from the group of permeability agents, plasticizers, wetting agents and surfactants, anti-

adhesives, flavouring agents, coloring agents and mixtures thereof.

Permeability agents, which may be mentioned are mannitol, lactose, water soluble polymers such as PVP, HPMC, HPC and polyethylene glycol.

Plasticizers, which may be mentioned are triethylcitrate, triacetine, stearic acid, dibutylsebacate, dibutylphthalate, glycerolmonostearate and polyethylene glycol.

Wetting agents and surfactants which may be mentioned are sodium laurylsulfate and polysorbates.

Anti-adhesives, which may be mentioned are magnesium stearate, talc, glycerolmonostearate, kaolin and Syloid™ .

Coloring agents, which may be mentiond are iron oxides.

Preferred coated particles according to the invention have a coating layer comprising Eudragit® EPO, stearic acid, magnesium stearate, sodiumlauryl sulfate, roflumilast, pharmaceutically acceptable salt of roflumilast, solvate or physiologically functional derivative thereof and mixtures thereof.

Based on the weight of the coated particles the amount of the carrier by weight is in the range of 50-95%, preferably in the range of 70-95%.

Based on the weight of the coated particles the amount of the polymer coating by weight (including the polymer and all other excipients except the active ingredient) is in the range of 3-20%.

Based on the weight of the coated particles the amount by weight of the active ingredient is in the range of 0.1-2%, preferably 0.2-0.8%.

The taste masking efficiency can be adjusted by variing the ratio by weight of the active ingredient to the polymer coating (including the polymer and all other excipients). Conveniently the ratio is in the range of 1:5 to 1:40, preferably 1:10 to 1:25.

The coated particle according to the invention may additionally contain further coating layer, preferably a second, outer coating layer (overcoating) based on a water soluble polymer and optionally additional excipients to improve wettability and dispersibility of the particles in water. Suitable water soluble polymers which can be used for such overcoating are e.g. hydroxypropylmethylcellulose, hydroxyproylcellulose, polyvinylpyrrolidone, polyethylene glycol and mixtures thereof.

Based on the weight of the over-coated particles the amount by weight of the overcoating is in the

range of 0.2-2%.

The coated particles according to the invention can be prepared by conventional techniques. To this end the active ingredient is suspended or dissolved in a coating polymer solution or dispersion optionally containing other suitable excipients. The polymer solution or dispersion can be on an aqueous base or on an organic base. Aqueous polymer solutions or dispersions are preferred. The polymer solution or dispersion can be prepared in a way known for those skilled in the area of pharmaceutical technology. The active ingredient is dispersed or dissolved within the polymer solution or dispersion. If necessary this can be done by stiring or the use of a turboemulsifier.
This solution/dispersion can then be sprayed on the carrier for example by applying a fluidized bed process with conventional bottom spray technique with a Wurster tube or by a top spray technique. This process is particularly preferred when using a carrier based on excipients in powder, or granule form. If a round shape of the particles is desired (eg to obtain a better mouth feel or better flowability) starter pellets made of cellulose or saccharose can be used as carrier instead of the powder blend or granulate. Due to the embedding of roflumilast within the polymer a masking of the unpleasant taste is effectively achieved without the need for a continuous polymer film.

Optionally a second outer polymer coating can be applied on the coated particles by the same process as described above. The polymer solution or dispersion can then be sprayed on the coated particles for example by applying a fluidized bed process with conventional bottom spray technique with a Wurster tube or by a top spray technique.

The advantage of the process described herein is that there is not a multi-stage process necessary for achieving the taste-masking, but that taste-masked coated particles can be prepared by a single process step.

Further subject of the invention is therefore a process for the manufacturing of coated particles according to the invention comprising the following steps:

(a) providing a suspension or solution of the active ingredient in a coating polymer solution or dispersion, optionally containing other suitable excipients
(b) spraying the solution or dispersion of step (a) on the carrier to obtain coated particles; and
(c) optionally spraying a polymer solution or dispersion on the coated particles as overcoating

The coated particles of the invention can then be used as basis for producing the dosage forms of the invention. The coated particles according to the invention can be either compressed to tablets, e.g. those that disintegrate rapidly in the mouth (orodispersible dosage form) or rapidly disperse in a glass of water. Alternatively the coated particles can be mixed with suitable excipients resulting in a powder for oral administration or for the preparation of a suspension for oral administration. These

formulations can be applied in single dose packages. They can be poured directly in the mouth for the application or they can be dispersed prior to the application in water. A preparation of a suspension from the powder prior to the treatment period is also possible. In this case, the suspension can be stored for e.g. a treatment period of two weeks.

Orodispersible dosage form in connection with the invention is to be understood as dosage form, which when placed in the oral cavity disperses rapidly before being swallowed. After disintegration in the oral cavity the tablet constituents are swallowed and the drug substance is absorbed in the gastro intestinal tract. In one embodiment the dosage form according to the invention is therefore a rapidly disintegrating dosage form in the form of an orodispersible tablet comprising an effective amount of the active ingredient in form of coated particles according to the invention together with excipients which, on oral intake of the dosage form, bring about rapid disintegration of the dosage form in the oral cavity, and, where appropriate, further excipients. The dosage form preferably has a maximum disintegration time in water (at 37°C) of 3 minutes, 2 minutes or 1 minute. (The disintegration time of the tablet can be determined according to standard procedures disclosed in pharmacopoeia monographs, preferably according to the European Pharmacopoeia 4th edition). Further examples of excipients which may be mentioned are fillers, carriers, disintegrants, binders, effervescence systems, lubricants, colouring agents, sweeteners, aromas, flavourings, pH-modifiers and surface-active substances. Fillers or carriers suitable in connection with the orodispersible tablet according to the invention are, in particular, fillers such as, calcium silicate (Rxipients®), sugar alcohols such as mannitol (e.g. Pearlitol® or Parteck® M, Merck, Germany), sorbitol (e.g. Karion®), xylitol, erythritol (e.g. Erythritol DC, Cerestar, Belgium), or maltitol, starches such as corn starch, potato starch and wheat starch, microcrystalline cellulose, saccharides such as glucose, lactose, sucrose and dextrose,co-processed fillers such as Pharmaburst®, SPI Pharma, USA, Starlac™, Meggle, Germany.

The content (in per cent by weight based on the finished dosage form) of filler in the tablet according to the invention is advantageously from 1 to 99% by weight. The content of filler is preferably from 30 to 95% by weight, and the content is particularly preferably from 40 to 80% by weight.

If appropriate, disintegrants can be added. Disintegrants suitable according to the invention are, in particular, insoluble polyvinylpyrrolidone (insoluble PVP, crospovidone), sodium carboxymethyl starch, sodium carboxymethylcellulose croscarmellose sodium, alginic acid, and starches able to fulfil the function of a disintegrant (e.g. Starch 1500).

The content (in per cent by weight based on a tablet according to the invention) of disintegrant in the orodispersible, rapidly disintegrating tablet according to the invention can usually be from 0.5 to 30% by weight. The content of disintegrant is preferably from 1 to 15% by weight. The content of

disintegrant is particularly preferably from 1 to 5% by weight.

Suitable lubricants, which may be mentioned are sodium stearyl fumarate, magnesium stearate, calcium stearate, stearic acid, talc and colloidal silica (Aerosil).

The content (in per cent by weight based on the finished dosage form) of lubricant in the rapidly disintegrating orodispersible tablet according to the invention is usually from 0.1 to 5% by weight. The content of lubricant is preferably from 0.2 to 3% by weight. The content of lubricant is particularly preferably from 0.5 to 2% by weight.

Binders suitable according to the invention are polyvinylpyrrolidone (PVP, Polyvidon® K25, Polyvidon® K90) or mixtures of PVP with polyvinyl acetate (e.g. Kollidon® 64), gelatin, corn starch paste, preswollen starches (Starch® 1500, Uni-Pure® WG220), hydroxypropylmethylcellulose (HPMC) or hydroxypropylcellulose (L-HPC).

The content (in per cent by weight based on the tablet according to the invention) of binder can be up to 10% by weight, and it can preferably be up to 5% by weight.

Suitable surface-active substances which may be mentioned are sodium lauryl sulfate or Tween® 20, Tween® 60 or Tween® 80.

It is also possible if desired for one or more flavours and sweeteners to be present in the dosage form according to the invention. It is possible thereby for example to achieve an improvement in taste. These substances are added in the usual amounts.

In a preferred embodiment of the invention, the orodispersible dosage form of the invention comprises coated particles of active ingredient, at least one filler, preferably on the basis of mannitol, optionally a disintegrant, a lubricant, a sweetener and a flavouring agent.

The orodispersible tablet can be produced by processes known to the skilled worker. The rapidly disintegrating tablet is preferably produced by

i) dry mixing of filler and/or disintegrant;
ii) production of granules of filler and binder and mixing of the granules with a disintegrant or
iii) dry granulation (briqueting or compacting) of one or more excipient components.

The coated particles are subsequently admixed to the mixtures obtained in i), ii) or iii) and then, if desired, flavors/flavoring substances and finally also one or more lubricants are admixed. The mixture obtained in this way can be compressed in a tablet press under conventional conditions.

In the case of dosage forms based on powders for oral administration or for the preparation of a suspension for oral administration, suitable excipients are, in particular, those excipients, which are normally used to produce suspensions. Particularly suitable according to the invention are excipients with which it is possible to produce a thickened base, such as thickeners. Examples of thickeners in connection with the invention are xanthan, substituted celluloses, polyvinylpyrrolidone (polyvidone types), sheet silicates, alginates, alginic acids or mixtures thereof. The proportion of thickener depends on the desired viscosity or consistency intended for the suspension ready for use. The proportion of xanthan, based on the suspension ready for use, is usually from 0.1 to 1% by weight. The proportion of substituted celluloses depends on the viscosity levels of the celluloses and is usually from 0.1 to 10% by weight based on the suspension ready for use. Examples of substituted celluloses of the invention, which may be mentioned are carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose or hydroxypropylcellulose. The proportion of polyvinylpyrrolidone (polyvidone types) is normally from 0.1 to 10% by weight based on the suspension ready for use. Sheet silicates such as the veegum or bentonites can be employed alone or in combination with water-soluble thickeners. The total proportion of thickener is then advantageously from 0.1 to 7% by weight based on the suspension ready for use. Alginates and alginic acid are usually added in a proportion of from 0.1 to 10% by weight based on the suspension ready for use. Further pharmaceutical excipients preferably employed are insoluble, crosslinked polyvinylpyrrolidone (crospovidones) and microcrystalline cellulose. It is observed in this case, that a loose sediment forms and prevents agglomeration of the individual active ingredient units. Microcrystalline cellulose and crospovidone are normally employed in a proportion of from 0.5 to 5% by weight based on the suspension ready for use..

Other suitable excipients, which may be present in the powder for oral administration or for the preparation of a suspension of the invention are, for example, flavoring substances (such as flavors and sweeteners), pH-modifiers, preservatives or else emulsifiers. Flavors are added in usual amounts. Other flavoring substances by way of example are acids such as citric acid, sweeteners such as saccharin, aspartame, cyclamate sodium or maltol, which are added according to the desired result. Examples of emulsifiers are lecithins, sodium lauryl sulfate, Tweens® or Spans, which are normally added in a proportion of from 0.01 to 1% by weight. Preservatives such as benzoic acid, salts of benzoic acid, methyl 4-hydroxybenzoate, propyl 4-hydroxybenzoate, sorbic acid or salts thereof might also be added if needed. The proportion depends on the preservative used and is normally from 0.1 to 4% by weight based on the suspension ready for use.

Depending on the polymer used for the coating of the particles (i.e. in the case of polymers which have a pH dependent solubility) it can be necessary to add pH-modifiers in order to prevent the

release of active ingredient in the suspension pior to administration. When basic polymers, such as Eudragit EPO or chitosan are used, the pH of the suspension preferably needs to be above pH 5. When an acidic polymer, such as Eudragit L, cellulose acetate phthalate or hydroxypropylmethylcellulose phthalate is used, the pH of the suspension preferably is below pH5. Suitable pH-modifiers are for example citric acid and its salts, tartaric acid and its salts, phosphoric acid and its salts and all other pharmacologically acceptable pH-modifiers.

The powder for the direct oral administration or for the preparation of the suspension of the invention is produced by techniques known to the skilled worker. Preferably the coated particles are blended with the other excipients. If single dose packages are the dosage form of choice, it might be also possible to fill first the coated granules into the sachet followed by the filling of the blend of the other excipients. Water is preferably used as dispersant for the preparation of the suspension prior to the use or prior to the treatment period.

The coated particles and the dosage forms according to the invention are described by way of examples below. The following examples explain the invention in more detail without restricting it.

Examples

1.Coated granules

1.1 Preparation of the granulation suspension

1.51g of sodium dodecylsulfate was dissolved in 125.87g of water by stirring. After 5min stirring 15.08g of Eudragit® EPO was suspended. After another 10min 2.26g of stearic acid was added and the suspension was stirred for at least 5 hours. 5.28g of magnesium stearate was added and suspended under stiring. Finally, 2.23g of roflumilast micronized were suspended.

1.2 Preparation of the coated granules

94.5g of microcrystalline cellulose, 94.5g of lactose monohydrate and 10.5 g of croscarmellose sodium were mixed in a fluidized bed granulator. 59.62g of the suspension prepared under 1.1 were sprayed upon the powder blend. In a typical process, the temperature of the fluidized powder is in the range of 25-35°C. The formulation avoids the numbness sensation normally observed, when the oral cavity is exposed to roflumilast formulations.

1.3 Preparation of granulation suspension and granulation

3.02g of sodium dodecylsulfate was dissolved in 251.74g of water by stirring. After 5min stirring 30.17g of Eudragit EPO was suspended. After another 10min 4.52g of stearic acid was added and the suspension was stirred for at least 5 hours. 10.56g of magnesium stearate was added and suspended under stiring. Finally, 2.23g of roflumilast micronized were suspended. 119.24g of the suspension was sprayed on a powder blend composed of 94.5g of microcrystalline cellulose, 94.5g of lactose monohydrate and 10.5 g of croscarmellose sodium in a fluidized bed apparatus.

1.4. Preparation of granulation suspension and granulation

10g of talcum was dispersed in 36.65g of water under stirring. 33.33g of Eudragit NE30D dispersion was added and mixed. Finally, 2.20g of roflumilast micronized has been added. 94.5g of microcrystalline cellulose, 94.5g of lactose monohydrate and 10.5 g of croscarmellose sodium were mixed in a fluidized bed granulator. 59.62g of the suspension were sprayed upon the powder blend.

2. Coated pellets

2.1 Preparation of pellets

118g of the suspension prepared under 1.1 was sprayed upon 190g of commercially available pellets made of cellulose (Cellets™) in a fluidized bed process. The size of the pellets was in the range of

100-200 µm and did not change significantly during the spraying process. The formulation avoids the numbness sensation normally observed, when the oral cavity is exposed to roflumilast formulations.

2.2. Preparation of pellets with additional overcoating

1.2g of HPMC 15cp was dissolved in 46.35g of water. 19.8g of the solution was sprayed on 39.1g of the coated pellets which were prepared according to 2.1. The pellets with overcoating can be dispersed easily in water without floating.

3. Dissolution Testing

Dissolution testing has been performed with the pellets prepared under 2.1. The dissolution conditions were the following:
Apparatus: USP paddle
Medium: Phosphate buffer pH6.8 + 0.1% SDS, 1000ml, 37°C
Rotation speed: 50rpm

The following amount of roflumilast was dissolved:

5min	2.3%
15min	8.7%
60min	35.0%

When the same dissolution testing has been performed under acidic conditions (0.1N-HCl +0.1% SDS) completed dissolution was obtained after 30min.

These data show that by the proposed manufacturing method a taste-masking can be obtained in the oral cavity, since the dissolution is low under neutral conditions.

4. Preparation of dosage forms

4.1 Preparation of orodispersible tablets

60g of the granulate according to 1.3 is blended with 234g of Pharmaburst™, 0.45 g of aspartame, 0.45g of acesulfame potassium and 0.6g of flavours. Finally 4.5g of magnesium stearate were added. The blend is compressed to tablets. The disintegration time was less than 2min.

4.2. Preparation of a powder for the preparation of an oral suspension.

3 g of xanthan, 12g of crospovidone, 55g of saccharose, 29.2g of mannitol, 0.3 g of sodium

laurylsulfate and 0.5g of flavour were blended. 6.2g of the over-coated pellets prepared under 2.2. were added. 1.00 g of the final blend was suspended in 20ml of water prior to the administration.

Industrial applicability

The dosage forms of the invention can be employed for the treatment and prevention of all diseases regarded as treatable or preventable through the use of PDE 4 inhibitors. Selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4) are suitable on the one hand as bronchial therapeutic agents (for the treatment of airway obstructions owing to their dilating effect but also owing to their effect increasing the respiratory rate and respiratory drive) and for eliminating erectile dysfunction owing to the vasodilating effect, but on the other hand especially for the treatment of disorders, especially of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the central nervous system, of the intestine, of the eyes and of the joints, which are promoted by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. The pharmaceutical preparations of the invention can therefore be used in human and veterinary medicine for example for the treatment and prophylaxis of the following diseases: acute and chronic (especially inflammatory and allergen-induced) airway disorders of various etiologies (bronchitis, allergic bronchitis, bronchial asthma, COPD); dermatoses (especially of a proliferative, inflammatory and allergic nature) such as, for example, psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoic eczema, lichen simplex, sunburn, pruritus in the genitoanal region, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and extensive pyodermas, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders based on excessive release of TNF an leukotrienes, e.g. disorders of the arthritic type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic states), disorders of the immune system (AIDS, multiple sclerosis), types of shock [septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)] and generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders based on allergic and/or chronic abnormal immunological reactions in the region of the upper airways (pharyngeal space, nose) and adjacent regions (paranasal sinuses, eyes), such as, for example, allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and nasal polyps; but also cardiac disorders which can be treated by PDE inhibitors, such as, for example, heart failure, or disorders which can be treated owing to the tissue-relaxant effect of PDE inhibitors, such as, for example, erectile dysfunction or colic of the kidneys and ureters connected with kidney stones; or else disorders of the CNS such as, for example, depressions or arteriosclerotic dementia.

The invention further relates to a method for the treatment of mammals, including humans, suffering from one of the abovementioned diseases. The method is characterized by administration of a therapeutically effective and pharmacologically suitable amount of roflumilast to the mammalian patient, roflumilast being present in a dosage form of the invention. The disease is preferably asthma or airway obstructions, especially COPD (= chronic obstructive pulmonary disease).

The dosage forms of the invention comprise the active ingredient in the dose customary for the treatment of the particular disease. The dosage of the active ingredient is of the order of magnitude customary for PDE inhibitors, it being possible to administer the daily dose in one or more dosage units. The normal dose on systemic therapy (oral) is between 0.001 mg and 3 mg per kilogram and day. Dosage forms preferred according to the invention contain from 0.01 mg to 5 mg of roflumilast, preferably from 0.05 mg to 2.5 mg, particularly preferably 0.1 mg to 0.5 mg of roflumilast per dosage unit. Examples of dosage form of the invention contain 0.1 mg, 0.125 mg, 0.25 mg and 0.5 mg of roflumilast per dosage unit. Normally, one or more than one dosage unit of the invention is administered once a day. If desired, it is also possible for one or more dosage units of the invention to be administered more than once a day.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

THE CLAIMS OF THE INVENTION ARE DEFINED AS FOLLOWS:

1. Coated particles comprising a suitable carrier and a coating layer surrounding the carrier, which coating layer comprises a suitable coating polymer selected from the group of polyvinylpyrrolidone (PVP), cellulosic polymers, acrylic polymers, methacrylic copolymers, starch polymer, chitosan or mixtures thereof, optionally further pharmaceutically acceptable excipients and an active ingredient selected from the group of roflumilast, pharmaceutically acceptable salt of roflumilast, solvate or physiologically functional derivative thereof and mixtures thereof, wherein the coated particle has a mean particle size less than or equal to 2 mm.

2. Coated particle according to claim 1, wherein the active ingredient is roflumilast.

3. Coated particle according to claim 1 or 2 having a mean particle size less than or equal to 1 mm.

4. Coated particle according to claim 3, having a mean particle size in the range from 100 to 400 µm.

5. Coated particle according to any one of claims 1 to 4, wherein the carrier is based on excipients selected from the group of mannitol, saccharose, lactose, lactose monohydrate, glucose, erythritol, xylitol, cellulose, microcrystalline cellulose, croscarmellose sodium, crospovidone and mixtures thereof.

6. Coated particle according to claim 5, wherein the carrier is in the form of a powder, granule, small bead, particle, pellet, starter pellet or nonpareil.

7. Coated particle according to any one of claims 1 to 6, wherein the coating polymer is selected from the group of ethylcellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropyl cellulose (HPC), cellulose acetate phthalate, hydroxypropylmethylcellulosephthalate, acrylate ammoniomethacrylate copolymer, ethylacrylate methylmethacrylate copolymer or mixtures thereof.

8. Coated particle according to any one of claims 1 to 7, wherein the coating polymer is a water-soluble polymer.

9. Coated particle according to claim 8, wherein the coating polymer is selected from the group of hydroxypropylmethylcellulose (HPMC), hydroxypropyl cellulose (HPC), or mixtures thereof.

2006224619 14 Oct 2011

10. Coated particle according to any one of claims 1 to 9, wherein the coating polymer shows a pH dependent water solubility.

11. Coated particle according to claim 10, wherein the coating polymer is swellable and permeable above pH 5 and soluble below pH 5.

12. Coated particle according to claim 10, wherein the coating polymer is a basic butylated methacrylate copolymer, which is a copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters.

13. Coated particle according to any one of claims 1 to 12, wherein roflumilast is suspended in the coating layer.

14. Coated particle according to claim 13, wherein the mean particle size of roflumilast suspended in the coating layer is in the range from 0.1 to 100 µm.

15. Coated particle according to claim 13, wherein the mean particle size of roflumilast suspended in the coating layer is in the range from 1 to 10 µm.

16. Coated particle according to claim 14 or 15, wherein the coating layer comprises further pharmaceutically acceptable excipients selected from the group of permeability agents, plasticizers, wetting agents and surfactants, anti-adhesives, flavouring agents, coloring agents and mixtures thereof.

17. Coated particle according to any one of claims 1 to 16, wherein the coating layer comprises methacrylic copolymer, stearic acid, magnesium stearate, sodiumlauryl sulfate and roflumilast.

18. Coated particle according to any one of claims 1 to 17, wherein the ratio by weight of the active ingredient selected from the group of roflumilast, pharmaceutically acceptable salt of roflumilast, solvate or physiologically functional derivative thereof and mixtures thereof to the polymer coating (including the polymer and all other excipients of the coating layer) is in the range of 1:5 to 1:40.

19. Coated particle according to any one of claims 1 to 17, wherein the ratio by weight of the active ingredient selected from the group of roflumilast, pharmaceutically acceptable salt of roflumilast, solvate or physiologically functional derivative thereof and mixtures thereof to the polymer coating (including the polymer and all other excipients of the coating layer) is in the range of 1:10 to 1:25.

20. Coated particle according to any one of claims 1 to 19, additionally containing an outer overcoating.

21. A process for producing a coated particle according to any one of claims 1 to 20, comprising the following steps:

(a) providing a suspension or solution of the active ingredient in a coating polymer solution or dispersion, optionally containing other suitable pharmaceutically acceptable excipients; and

(b) spraying the solution or dispersion of step (a) on the carrier; and

(c) optionally spraying a polymer solution or dispersion on the coated particles of step (b).

22. Process according to claim 21, wherein in step (a) an aqueous suspension or solution is provided.

23. Process according to claim 21 or 22, wherein spraying is carried out applying a fluidized bed process with a Wurster tube or top spray technique.

24. Dosage form comprising a therapeutically effective amount of an active ingredient selected from the group of roflumilast, pharmaceutically acceptable salt of roflumilast, solvate or physiologically functional derivative thereof and mixtures thereof in the form of coated particles according to any one of claims 1 to 20 together with one or more pharmaceutically acceptable excipients.

25. Dosage form according to claim 24, which is a tablet, a powder for oral administration or a suspension for oral administration.

26. Dosage form according to claim 24 or 25, which is an orodispersible dosage form.

27. A method for the treatment or prophylaxis of a disease regarded as treatable or preventable by PDE 4 inhibitors, wherein a dosage form as claimed in any one of claims 24 to 26 is administered.

28. Use of the coated particles according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment or prophylaxis of a disease regarded as treatable or preventable by PDE 4 inhibitors.

29. Coated particles as defined in claim 1, processes for producing them, dosage forms containing them or methods or uses involving them, substantially as herein described with reference to the accompanying examples.