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(54) PACKAGE FOR MULTIPLE DOSE INHALATORS HAVING OPTIMISED EMPTYING PROPERTIES

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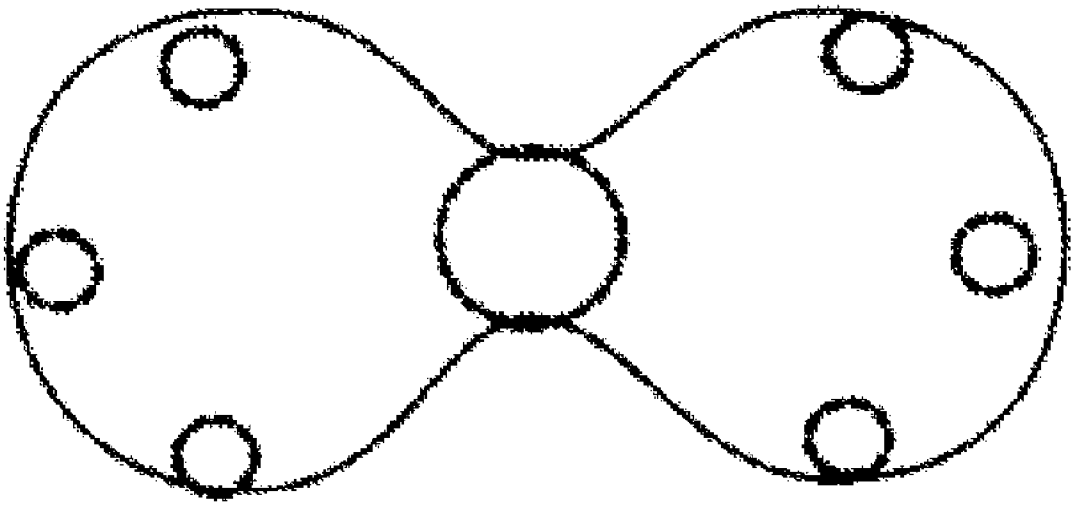
(57) **ABSTRACT**

The invention relates to a package for pharmaceutical compositions, mixtures or formulations for use in a powder inhaler.



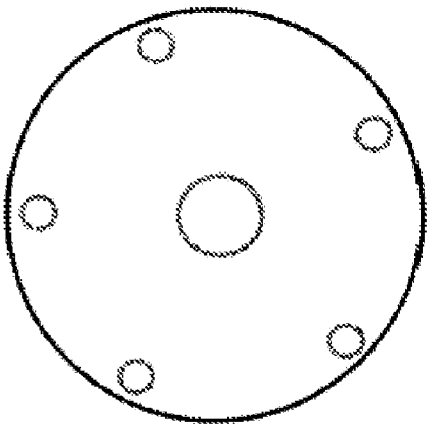


Fig. 1

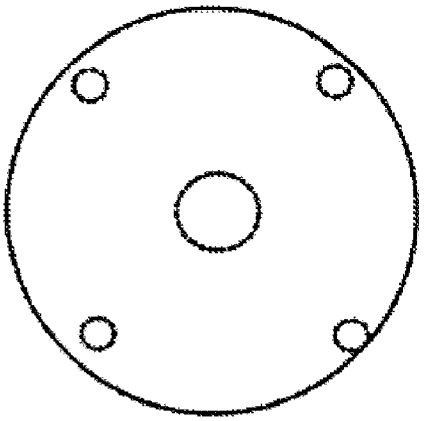


Fig. 2

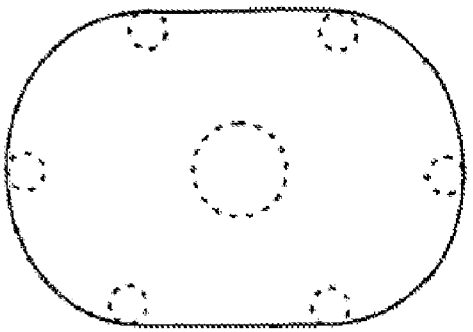


Fig. 3

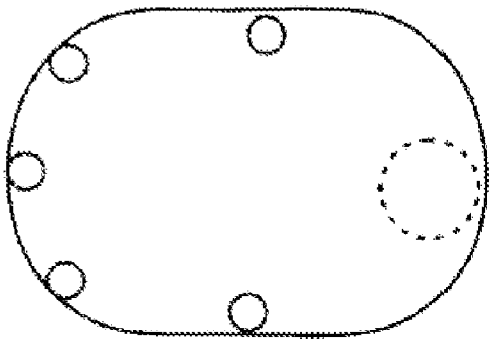


Fig. 4

Fig. 5

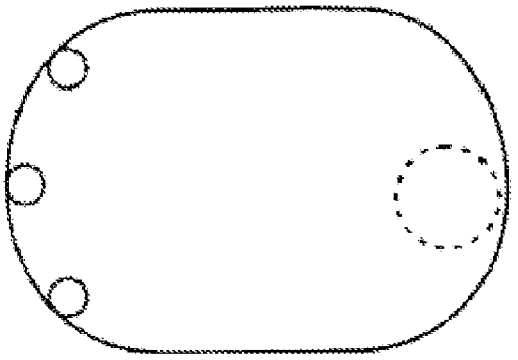


Fig. 6

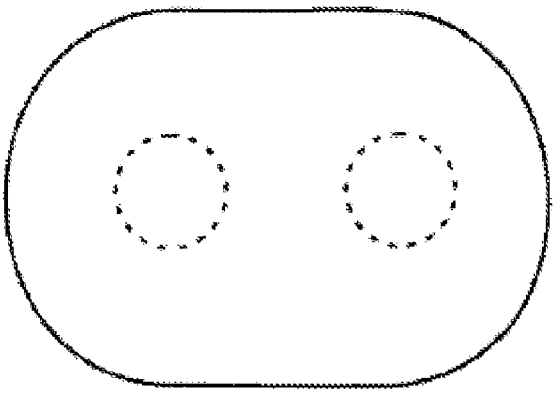


Fig. 7

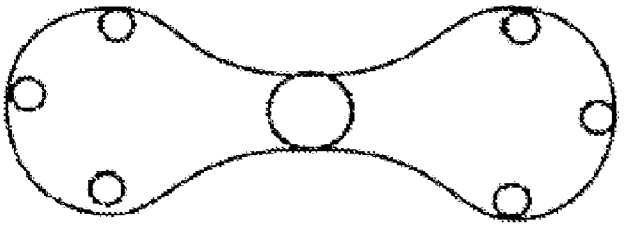


Fig. 8

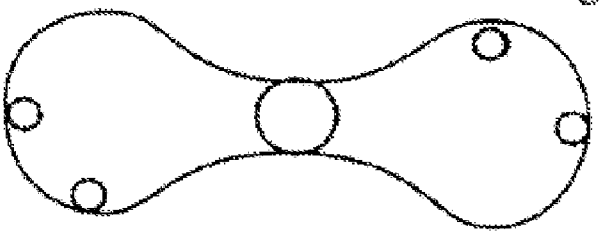


Fig. 9

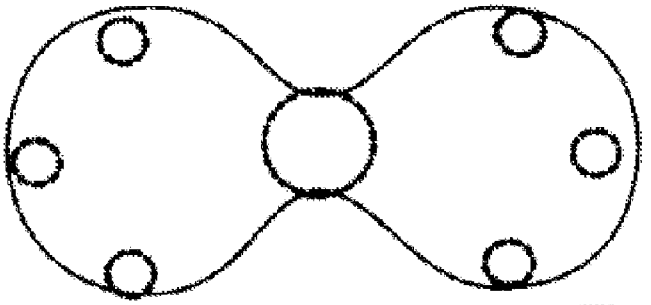


Fig. 10

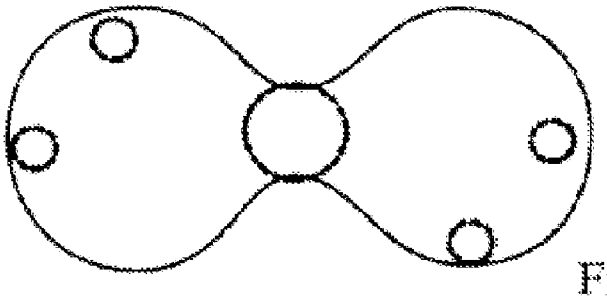


Fig. 11

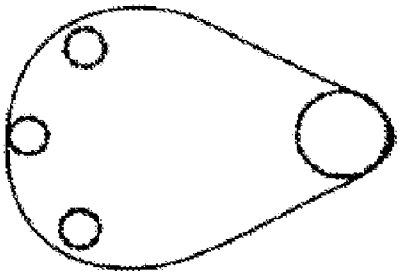


Fig. 12

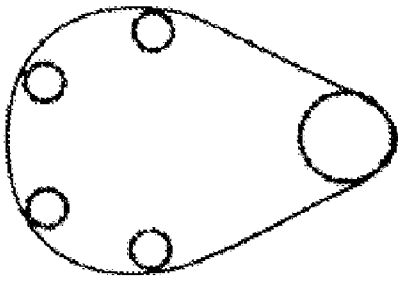
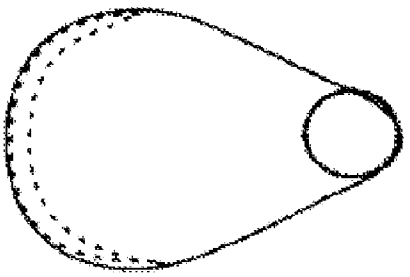


Fig. 13



PACKAGE FOR MULTIPLE DOSE INHALATORS HAVING OPTIMISED EMPTYING PROPERTIES

BACKGROUND OF THE INVENTION

[0001] This application claims priority of DE 10 2006 014 434, which application is incorporated herein by reference in its entirety.

[0002] 1. Field of the Invention

[0003] The invention relates to a package for pharmaceutical compositions, mixtures or formulations for use in a powder inhaler.

[0004] 2. Description of the Prior Art

[0005] Medical aerosol therapy intended for pulmonary inhalation using nebulisers, metered-dose aerosols or powder inhalers plays an important part in the treatment of numerous lung diseases.

[0006] In the field of powder inhalers, single-dose and multi-dose devices are known. The multi-dose powder inhalers contain the pharmaceutical composition, mixture or formulation either in the form of a powder supply from which the single dose is taken from a well by means of a built-in metering unit, or pre-metered packaged single doses which are either stored together in the device (e.g., in the form of packaged amounts in blisters) or are placed individually in the device for use (e.g., in the form of capsules).

[0007] In multi-dose powder inhalers, in particular, the manner of packaging in which the powder formulation is present in the device is critical to the quality of the product and hence to its suitability for use by inhalation.

[0008] Therefore, a chief objective of the packaging is to keep the chemical composition of the atmosphere inside the packaging constant, in order to prevent physical or chemical changes to the pharmaceutical composition, mixture or formulation, or to stabilise them.

[0009] In this context a distinction is made between stability directed to the short term, which the pharmaceutical composition, mixture or formulation has to have per se, even if it is not adequately protected by the packaging ("in-use stability") and the long-term stability, i.e., the stability which has to be guaranteed for as long as the pharmaceutical composition, mixture or formulation is contained in the unopened package.

[0010] It is also important that the patient receives the correct dose of the inhalable formulation on inhaling.

[0011] The term "fine particle dose" refers to the dose that reaches the patient's lungs. The fine particle dose is influenced by the interactions of the micronised particles of active substance with one another and also the interactions with the excipients.

[0012] It is also known that particularly as a result of variations in the level of moisture in the interior of the packaging these interactions may increase such that the fine particle dose is significantly reduced. Such changes include the penetration of water into the package and also the elimination of water from the inside of the package.

[0013] It is also necessary for a package to have a shape and an opening pattern (i.e., the places in the packaging which allow the blister to be opened by piercing or cutting) which enable an optimum air supply and hence optimum delivery of the pharmaceutical composition, mixture, or formulation.

[0014] Examples of multi-dose powder inhalers are known in the art. They are known for example from EP 0 703 800 B1 or EP 0 911 047 A1, which disclose a powder inhaler consisting of a cup-shaped lower part and an equally cup-shaped lid. After placing the capsule in the capsule holder, the patient can press an actuating member which is movable from a resting position and thereby interacts with at least one pin that can be pressed into the capsule holder. The capsule is pierced by the pin or pins and the drug is released. Thus, for example, DE 3348370 and DE 3336486 further disclose inhalers which contain a disc-shaped blister pack comprising a number of wells arranged in a circle. The individual wells each contain a dose of a medicament powder intended for inhalation. The wells are closed off on both sides by a sealing film, for example. To deliver the medicament powder the cavity is opened. An air channel connects the opened well with the mouthpiece of the inhaler. By way of example the inhaler of DE 3336486 will be described in more detail. It comprises a housing in which there is a chamber (supply chamber) comprising an air inlet and in which there is a disc-shaped round blister with medicament pouches packed therein. The blister is loosely connected to a rotatable round disc. Around the disc are formed holes which are axially in contact with the medicament pouches, i.e., the pouches and holes are located above and below one another. The chamber has an air outlet. The inhaler also has a piston which is arranged so that it can open a pouch of medicament by piercing it, so that the medicament is released into the chamber and can be breathed in through a mouthpiece. Reference is made to the drawings in the patent application and US patent specification.

[0015] With regard to the packaging of medicament powders, a distinction is made between the primary packaging and the secondary packaging. The primary packaging is characterized in that it is in direct contact with the inhalable formulation. The primary packaging may optionally be surrounded by a second, outer protection, the secondary packaging. The primary packaging may be, for example, a capsule, a solid or flexible blister with wells or a disc comprising wells.

[0016] The secondary packaging may be a blister, a pouch, a bag or other container. The secondary packaging generally totally encloses the primary packaging. Secondary packaging is used particularly when the primary packaging does not provide adequate protection from moisture.

[0017] The primary packaging and optionally the secondary packaging have the task of protecting the active substance and also the entire inhalable formulation from chemical or physical change, so that it remains stable for long periods. The physical changes in question may be, in particular, changes which might affect the delivery of the intended dose of fine particles.

[0018] The choice of a suitable material for the packaging is determined by two factors. On the one hand the material must be able to perform the protective function required. On the other hand the material must be such that the packaging can be made into the form needed for use in the powder inhaler and can perform the function expected of it.

[0019] The problem underlying the present invention is to optimise the shape of the packaging, the piercing pattern of

the packaging and the fill level of a pharmaceutical composition, mixture or formulation, so as to improve the delivery of a pharmaceutical composition, mixture or formulation.

SUMMARY OF THE INVENTION

[0020] This problem is solved by a package according to claim 1. Advantageous further features are the subject-matter of the subsidiary claims.

[0021] The present invention therefore relates to packages for inhalable powders, which are optimised in their shape, piercing pattern and fill level with a pharmaceutical composition, mixture or formulation.

BRIEF DESCRIPTION OF THE INVENTION

[0022] The Figures show, by way of example, the different shapes of a capsule or of an individual well of a blister (known over all as packaging means) and the corresponding piercing positions.

[0023] The Figures serve to illustrate the invention without restricting its scope.

[0024] FIG. 1: sphere or hemisphere, 5 hole-shaped inlet openings, 1 outlet

[0025] FIG. 2: sphere or hemisphere, 4 hole-shaped inlet openings, 1 outlet

[0026] FIG. 3: oval shape, 6 hole-shaped inlet openings, 1 outlet

[0027] FIG. 4: oval shape, 5 hole-shaped inlet openings, asymmetrical, 1 outlet

[0028] FIG. 5: oval shape, 3 hole-shaped inlet openings, asymmetrical, 1 outlet

[0029] FIG. 6: oval shape, 2 hole-shaped inlet openings

[0030] FIG. 7: bone-shaped, 2×3 hole-shaped inlet openings, 1 outlet

[0031] FIG. 8: bone-shaped, 2×2 hole-shaped inlet openings, asymmetrical, 1 outlet

[0032] FIG. 9: figure-of-eight shape, 2×3 hole-shaped inlet openings, 1 outlet

[0033] FIG. 10: figure-of-eight shape, 2×2 hole-shaped inlet openings, asymmetrical, 1 outlet

[0034] FIG. 11: teardrop-shape, 3 hole-shaped inlet openings, 1 outlet

[0035] FIG. 12: teardrop-shape, 4 hole-shaped inlet openings, 1 outlet

[0036] FIG. 13: teardrop-shape, crescent-shaped inlet, 1 outlet

DETAILED DESCRIPTION OF THE INVENTION

[0037] The invention relates to optimised packages as described above which allow improved air flow and hence improved delivery of a pharmaceutical composition, mixture or formulation by virtue of the shape of their opening pattern in their piercing pattern and the fill level with the pharmaceutical composition, mixture or formulation. Preferably the packages consist of a capsule, a blister, a blister disc or a blister strip. These different forms (with the exception of the capsules) will hereinafter be referred to over all as blisters.

[0038] The capsule generally consists of two parts, a capsule body (body) and a capsule cap (cap), which fit telescopically inside one another. However, multi-part capsules are also known. It is preferable to use size 2-4 capsules, most preferably size 3 capsules.

[0039] The capsule material is non-digestible plastics or gelatine, particularly hard gelatine.

[0040] The blister disc may be, for example, a cylinder-like disc up to 5 mm high and up to 15 cm in diameter. In the disc are depressions or holes (wells) formed perpendicularly to the plane of the disc. A disc of this kind may for example be placed in an inhaler according to DE 3348370 or DE 3336486. An inhaler of this kind has a housing which contains the disc-shaped round blister with medicament pouches packed therein. The inhaler comprises, inter alia, a pin which is arranged so that it can open one medicament pouch, so that the medicament is released into the chamber and can be breathed in through a mouthpiece.

[0041] The shape of the package according to the invention including the shape of the well is fundamentally determined by the powder inhaler which is to be used. Preferably, the packaging is teardrop-shaped or oval or in the shape of a figure of eight. The inflow surfaces and outflow surface(s) are as far away from one another as possible.

[0042] The package which is a blister first of all comprises a base element consisting of a thermoplastic plastics and at least two wells separated from one another by a web. The wells are open at least on one side, possible on two opposing sides. These openings are closed off in the packaging ready for use, e.g., by means of a sealing foil which is attached to the base element.

[0043] The package may consist of standard commercial materials. Preferably, it consists of a plastics material. Most preferably, the materials used as plastics selected from among the thermoplastic polymers such as, e.g., polystyrenes, polyolefins, polyamides, polyvinyl chlorides, polyethylenes, polycarbonate, polyester, polypropylene, polyethylene terephthalate or polyurethane. These have the necessary rigidity or mobility to enable them to perform the mechanical tasks of the primary packaging. Also suitable are, for example, natural substances such as gelatine or composite materials of plastics and metals, such as aluminium.

[0044] According to the invention it is not essential, though preferable, that all the walls of the well should consist of the same material. In a well, at least the wall that closes off the opening may be made of a different material from the other walls.

[0045] Further information regarding the composition or processing can be found in the prior art, particularly EP599690, EP432438 or EP400460.

[0046] The fill level of the pharmaceutical composition, mixture or formulation in the package can be optimised and will depend on the flowability of the pharmaceutical composition, mixture or formulation.

[0047] The term flowability indicates the ability of the pharmaceutical composition, mixture or formulation to flow

easily as a loose material. In the art the flowability ff_c is defined as follows:

$$ff_c=\sigma_1/\sigma_c.$$

[0048] Here, σ_1 is the solidification tension and σ_c is the bulk strength. Normally the flowability is determined using a ring shear device.

[0049] For pharmaceutical compositions, mixtures, or formulations with poor to no flowability, the flowability accords with the following: $4 \geqq ff_c > 1$. In this case, packages are used which are partly filled, such that there is a free passage for air between at least one inlet opening and an outlet opening. For readily flowable pharmaceutical compositions, formulations or mixtures the formula for the flowability is $4 < ff_c$. In this case, packages which are partly filled are used, such that there is a free passage of air between at least one inlet opening and an outlet opening, or which are completely filled so that an advantageous (simple and inexpensive) filling process can be used. In the latter case, the fill volume is determined by the shape of the packaging and there is no need for any special metering process.

[0050] Examples of pharmaceutical compositions, formulations or mixtures include all the inhalable compounds, such as, e.g., inhalable macromolecules, as disclosed in EP 1 003 478.

[0051] The compounds listed below may be used in the device according to the invention on their own or in combination. In the compounds mentioned below, W is a pharmacologically active substance and is selected (for example) from among the betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists, and P13-kinase inhibitors. Moreover, double or triple combinations of W may be combined and used in the device according to the invention. Combinations of W might be, for example:

[0052] W denotes a betamimetic, combined with an anticholinergic, corticosteroid, PDE4-inhibitor, EGFR-inhibitor or LTD4-antagonist,

[0053] W denotes an anticholinergic, combined with a betamimetic, corticosteroid, PDE4-inhibitor, EGFR-inhibitor or LTD4-antagonist,

[0054] W denotes a corticosteroid, combined with a PDE4-inhibitor, EGFR-inhibitor or LTD4-antagonist

[0055] W denotes a PDE4-inhibitor, combined with an EGFR-inhibitor or LTD4-antagonist

[0056] W denotes an EGFR-inhibitor, combined with an LTD4-antagonist.

[0057] The compounds used as betamimetics are preferably compounds selected from among albuterol, arformoterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salmefamol, salmeterol, soterenol, sulphonterol, terbutaline, tiaramide, tolubuterol, zinterol, CHF-1035, HOKU-81, KUL-1248, and

[0058] 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzyl-sulphonamide

[0059] 5-[2-(5.6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one

[0060] 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone

[0061] 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol

[0062] 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino] ethanol

[0063] 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol

[0064] 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino] ethanol

[0065] 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol

[0066] 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol

[0067] 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one

[0068] 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol

[0069] 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4] oxazin-3-one

[0070] 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one

[0071] 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo [1,4]oxazin-3-one

[0072] 8-{2-[1,1 -dimethyl-2-(2.4.6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1, 4]oxazin-3-one

[0073] 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4] oxazin-3-one

[0074] 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1.1dimethyl-ethylamino]-ethyl}-4H-benzo[1, 4]oxazin-3-one

[0075] 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4] oxazin-3-one

[0076] 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4] oxazin-3-one

[0077] 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3.4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid

[0078] 8-{2-[2-(3.4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0079] 1-(4-ethoxy-carbonylamino-3-cyano-5-fluorophenyl)-2-(tert-butylamino)ethanol

[0080] 2-hydroxy-5-(1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-benzaldehyde

[0081] N-[2-hydroxy-5-(1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-phenyl]-formamide

[0082] 8-hydroxy-5-(1-hydroxy-2-{2-[4-(6-methoxy-biphenyl-3-ylamino)-phenyl]-ethylamino}-ethyl)-1H-quinolin-2-one

[0083] 8-hydroxy-5-[1-hydroxy-2-(6-phenethylamino-hexylamino)-ethyl]-1H-quinolin-2-one

[0084] 5-[2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one

[0085] [3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-5-methyl-phenyl]-urea

[0086] 4-(2-{6-[2-(2.6-dichloro-benzyloxy)-ethoxy]-hexylamino}-1-hydroxy-ethyl)-2-hydroxymethyl-phenol

[0087] 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzyl-sulphonamide

[0088] 3-(3-{7-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-heptyloxy}-propyl)-benzyl-sulphonamide

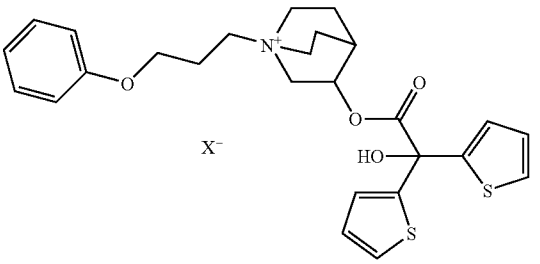
[0089] 4-(2-{6-[4-(3-cyclopentanesulphonyl-phenyl)-butoxy]-hexylamino}-1-hydroxy-ethyl)-2-hydroxymethyl-phenol

[0090] N-Adamantan-2-yl-2-(3-{2-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl}-phenyl)-acetamide optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

[0091] The anticholinergics used are preferably compounds selected from among the tiotropium salts, preferably the bromide salt, oxitropium salts, preferably the bromide salt, flutropium salts, preferably the bromide salt, ipratropium salts, preferably the bromide salt, glycopyrronium salts, preferably the bromide salt, trospium salts, preferably the chloride salt, tolterodine. In the above-mentioned salts the cations are the pharmacologically active constituents. As anions the above-mentioned salts may preferably contain the chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate, while chloride, bromide, iodide, sulphate, methanesulphonate or p-toluenesulphonate are preferred as counter-ions. Of all the salts the chlorides, bromides, iodides, and methanesulphonates are particularly preferred.

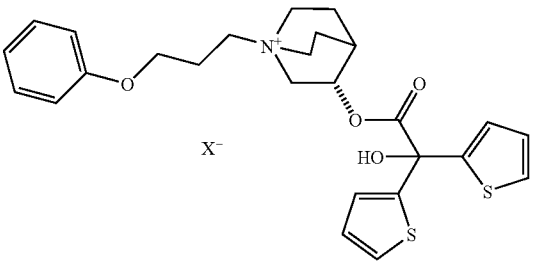
[0092] Other preferred anticholinergics are selected from among the salts of formula AC-1

AC-1



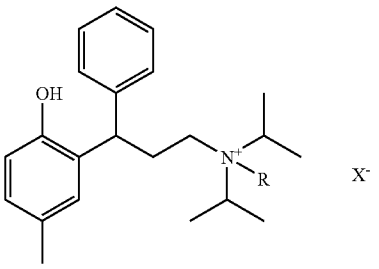
wherein X^- denotes an anion with a single negative charge, preferably an anion selected from among the fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate, preferably an anion with a single negative charge, particularly preferably an anion selected from among the fluoride, chloride, bromide, methanesulphonate and p-toluenesulphonate, particularly preferably bromide, optionally in the form of the racemates, enantiomers or hydrates thereof. Of particular importance are those pharmaceutical combinations which contain the enantiomers of formula AC-1-en

AC-1-en



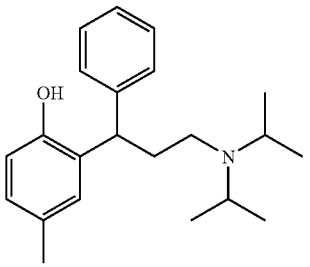
wherein X^- may have the above-mentioned meanings. Other preferred anticholinergics are selected from the salts of formula AC-2

AC-2



wherein R denotes either methyl or ethyl and wherein X^-may have the above-mentioned meanings. In an altemativen embodiment the compound of formula AC-2 may also be present in the form of the free base AC-2-base.

AC-2-base



[0093] Other specified compounds are:

[0094] tropenol 2,2-diphenylpropionate methobromide,

[0095] scopine 2,2-diphenylpropionate methobromide,

[0096] scopine 2-fluoro-2,2-diphenylacetate methobromide,

[0097] tropenol 2-fluoro-2,2-diphenylacetate methobromide;

[0098] tropenol 3,3',4,4'-tetrafluorobenzilate methobromide,

[0099] scopine 3,3',4,4'-tetrafluorobenzilate methobromide,

[0100] tropenol 4,4'-difluorobenzilate methobromide,

[0101] scopine 4,4'-difluorobenzilate methobromide,

[0102] tropenol 3,3'-difluorobenzilate methobromide,

[0103] scopine 3,3'- difluorobenzilate methobromide;

[0104] tropenol 9-hydroxy-fluorene-9-carboxylate methobromide;

[0105] tropenol 9-fluoro-fluorene-9-carboxylate methobromide;

[0106] scopine 9-hydroxy-fluorene-9-carboxylate methobromide;

[0107] scopine 9-fluoro-fluorene-9-carboxylate methobromide;

[0108] tropenol 9-methyl-fluorene-9-carboxylate methobromide;

[0109] scopine 9-methyl-fluorene-9-carboxylate methobromide;

[0110] cyclopropyltropine benzilate methobromide;

[0111] cyclopropyltropine 2,2-diphenylpropionate methobromide;

[0112] cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide;

[0113] cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide;

[0114] cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide;

[0115] cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide;

[0116] cyclopropyltropine methyl 4,4'-difluorobenzilate methobromide.

[0117] tropenol 9-hydroxy-xanthene-9-carboxylate methobromide;

[0118] scopine 9-hydroxy-xanthene-9-carboxylate methobromide;

[0119] tropenol 9-methyl-xanthene-9-carboxylate -methobromide;

[0120] scopine 9-methyl-xanthene-9-carboxylate -methobromide;

[0121] tropenol 9-ethyl-xanthene-9-carboxylate methobromide;

[0122] tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide;

[0123] scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide,

[0124] The above-mentioned compounds may also be used as salts within the scope of the present invention, wherein instead of the methobromide the salts metho-X are used, wherein X may have the meanings given hereinbefore for X^-.

[0125] As corticosteroids it is preferable to use compounds selected from among beclomethasone, betamethasone, budesonide, butixocort, ciclesonide, deflazacort, dexamethasone, etiprednol, flunisolide, fluticasone, loteprednol, mometasone, prednisolone, prednisone, rofleponide, triamcinolone, RPR-106541, NS-126, ST-26, and

[0126] (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1, 4-diene-17-carbothionate

[0127] (S)-(2-oxo-tetrahydro-furan-3S-yl)6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxy-androsta-1,4-diene-17-carbothionate,

[0128] cyanomethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tertamethylcyclopropyl-carbonyl)oxy-androsta-1,4-diene-17β-carboxylate optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof. Any reference to steroids includes a reference to any salts or derivatives, hydrates or solvates thereof which may exist. Examples of possible salts and derivatives of the steroids may be: alkali metal salts, such as for example sodium or potassium salts, sulphobenzoates, phosphates, isonicotinates, acetates, dichloroacetates, propionates, dihydrogen phosphates, palmitates, pivalates, or furoates.

[0129] PDE4-inhibitors which may be used are preferably compounds selected from among enprofyllin, theophyllin, roflumilast, ariflo (cilomilast), tofimilast, pumafentrin, lirimilast, arofyllin, atizoram, D-4418, Bay-198004, BY343, CP-325.366, D-4396 (Sch-351591), AWD-12-281 (GW-842470), NCS-613, CDP-840, D-4418, PD-168787, T-440,

T-2585, V-11294A, C1-1018, CDC-801, CDC-3052, D-22888, YM-58997, Z-15370, and

[0130] N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide

[0131] (−)p-[(4αR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[s][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide

[0132] (R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone

[0133] b 3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone

[0134] cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]

[0135] 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)cyclohexan-1-one

[0136] cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]

[0137] (R)-(+)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate

[0138] (S)-(−)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate

[0139] 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3.4-c]-1,2,4-triazolo[4.3-a]pyridine

[0140] 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3.4-c]-1,2,4-triazolo[4.3-a]pyridine

optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof. According to the invention the acid addition salts of the PDE4 inhibitors are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate, and hydro-p-toluenesulphonate.

[0141] The LTD4-antagonists used are preferably compounds selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001,MEN-91507 (LM-1507), VUF-5078, VUF-K-8707, L-733321 and

[0142] 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropane-acetic acid,

[0143] 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropaneacetic acid

[0144] [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof. According to the invention these acid addition salts are preferably selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate, and hydro-p-toluenesulphonate. By salts or derivatives which the LTD4-antagonists may optionally be capable of forming are meant, for example: alkali metal salts, such as for example sodium or potassium salts, alkaline earth metal salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates, or furoates.

[0145] EGFR-inhibitors which may be used are preferably compounds selected from among cetuximab, trastuzumab, ABX-EGF, Mab ICR-62, and

[0146] 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1 -yl]amino}-7-cyclopropylmethoxy-quinazoline

[0147] 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]-amino}-7-cyclopropylmethoxy-quinazoline

[0148] 4-[(3 -chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

[0149] 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline

[0150] 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

[0151] 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

[0152] 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

[0153] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline

[0154] 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

[0155] 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten1-yl]amino}-7-cyclopropylmethoxy-quinazoline

[0156] 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

[0157] 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 amino }-7-cyclopentyloxy-quinazoline

[0158] 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

[0159] 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N, N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazo line

[0160] 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N, N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazo line

[0161] 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

[0162] 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl] amino}-7-cyclopentyloxy-quinazoline

[0163] 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

[0164] 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N, N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydro furan-2-yl)methoxy]-quinazo line

[0165] 4-[(3-ethynyl-phenyl)amino]-6.7-bis-(2-methoxy-ethoxy)-quinazoline

[0166] 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinyl-carbonyl)amino]-quinazoline

[0167] 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

[0168] 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl] amino}-7-ethoxy-quinoline

[0169] 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl] amino }-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline

[0170] 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl] amino}-7-methoxy-quinazoline

[0171] 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline

[0172] 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N, N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline

[0173] 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5.5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl] amino}-quinazoline

[0174] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2.2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline

[0175] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2.2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline

[0176] 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2.2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline

[0177] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline

[0178] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline

[0179] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline

[0180] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-yloxy)-7-methoxy-quinazoline

[0181] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline

[0182] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline

[0183] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline

[0184] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{ 1-[(methoxymethyl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline

[0185] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline

[0186] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline

[0187] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline

[0188] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline

[0189] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline
4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline

[0190] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline

[0191] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline

[0192] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetylamino-ethoxy)-quinazoline

[0193] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline

[0194] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1 -[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

[0195] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline

[0196] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline

[0197] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazo line

[0198] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline

[0199] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline

[0200] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline

[0201] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline

[0202] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline

[0203] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline

[0204] 4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline

[0205] 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline

[0206] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazo line

[0207] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazo line

[0208] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline

[0209] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

[0210] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline

[0211] 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline

[0212] 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline

[0213] 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline

[0214] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline

[0215] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline

[0216] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline

[0217] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline

[0218] 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline

[0219] 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline

[0220] 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

[0221] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

[0222] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

[0223] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S, S)-(2-oxa-5-aza-bicyclo[2,2, 1]hept-5-yl)carbonyl]-piperidin-4-yloxy }-7-methoxy-quinazo line

[0224] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-pip eridin-4-yloxy}-7-methoxy-quinazo line

[0225] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline

[0226] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

[0227] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

[0228] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline

[0229] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline

[0230] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline

[0231] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline

[0232] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline

[0233] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline

[0234] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2.2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline

[0235] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline

[0236] 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention these acid addition salts are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate, and hydro-p-toluenesulphonate.

[0237] The dopamine agonists used are preferably compounds selected from among bromocriptin, cabergoline, alpha-dihydroergocryptine, lisuride, pergolide, pramipexol, roxindol, ropinirol, talipexol, tergurid, and viozan, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention these acid addition salts are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate, and hydro-p-toluenesulphonate.

[0238] H1-Antihistamines which may be used are preferably compounds selected from among epinastine, cetirizine, azelastine, fexofenadine, levocabastine, loratadine, mizolastine, ketotifen, emedastine, dimetindene, clemastine, bamipine, cexchlorpheniramine, pheniramine, doxylamine, chlorophenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastine, desloratidine, and meclozine, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates, or hydrates thereof. According to the invention these acid addition salts are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate, and hydro-p-toluenesulphonate.

[0239] It is also possible to use inhalable macromolecules, as disclosed in EP 1 003 478.

[0240] In addition, the compounds may come from the groups of ergot alkaloid derivatives, the triptans, the CGRP-inhibitors, the phosphodiesterase-V inhibitors, optionally in the form of the racemates, enantiomers, or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts, the solvates, and/or hydrates thereof.

[0241] Examples of ergot alkaloid derivatives are dihydroergotamine and ergotamine.

[0242] For inhalation, suitable substances include pharmaceutical compositions, pharmaceutical formulations and mixtures with the above-mentioned active substances, as well as the salts and esters thereof and combinations of these active substances, salts, and esters.

EXAMPLE

[0243] The emptying properties were determined using a standard powder (glass beads) by measuring the time taken for emptying a given constant flow by volume (corresponding to 10 L/min of air). Table 1 shows the emptying time of the different shapes of capsules or blisters. The inlet openings are shown in the drawings as small circles while the outlet openings are shown as large circles.

TABLE 1

type	name	emptying time (s)
1	sphere or hemisphere, 5 inlets	>100
2	sphere or hemisphere, 4 inlets	>100
3	oval shape, 6 inlets	57
4	oval shape, 5 inlets, asymmetrical	10
5	oval shape, 3 inlets, asymmetrical	2.2
6	oval shape, 2 holes	>100
7	bone, 2 × 3 inlets	38
8	bone, 2 × 2 inlets, asymmetrical	2.7
9	figure-of-eight, 2 × 3 inlets	>100
10	figure-of-eight, 2 × 2 inlets, asymmetrical	>100
11	teardrop, 3 inlets	2.9
12	teardrop, 4 inlets	2.4
13	teardrop, crescent-shaped inlet	1.7

[0244] The results in Table 1 show that the emptying properties of a package depend to a considerable extent on its shape and opening or openings.

TABLE 2

	residue after emptying (%)			emptying time (seconds)		
Name	micronised fenoterol	fenoterol powder mixture	tiotropium powder mixture	micronised fenoterol	fenoterol powder mixture	tiotropium powder mixture
1	88.63	84.02	46.896	8.46	7.91	6.8
2	87.04	87.58	45.832	9.35	7.42	6.44
3	52.95	39.28	13.936	4.29	3.13	3.46
4	29.93	23.49	5.744	1.19	1.27	1.66
5	32.88	16.37	11.408	1.2	1.31	1.03
6	80.25	71.81	33.816	6.95	6.53	5.63
7	51.37	33.93	20.56	3.95	3.18	2.92

TABLE 2-continued

	residue after emptying (%)			emptying time (seconds)		
Name	micronised fenoterol	fenoterol powder mixture	tiotropium powder mixture	micronised fenoterol	fenoterol powder mixture	tiotropium powder mixture
8	38.39	19.33	13.216	1.71	1.41	0.86
9	71.6	57.52	31.56	5.7	4.76	4.23
10	68.69	54.36	28.608	5.85	4.03	5.24
11	38.07	22.15	8.304	2.21	1.82	0.93
12	37.73	9.78	6.984	1.85	1.27	0.3
13	34.36	10.81	5.12	0.69	0.35	0.6

[0245] The flow rate of the air through the package of standard commercial size: 10 litres per minutes

[0246] The active substance in micronised form has a particle size of 1-5 μm. As well as the active substance the powder mixture also contains lactose 200 m.

[0247] The results of Table 2 show, for the active substances fenoterol and tiotropium

[0248] a) the residue left in the well, and

[0249] b) the emptying time of the well.

[0250] A well of a package which has an optimum air flow by reason of its shape and opening patter has significantly enhanced emptying properties. The following formula applies to the ratio V (sum of the inflow surfaces divided by the sum of the outflow surfaces): $0.5<V<2$. Preferably the sum of the inflow surfaces should be equal to the sum of the outflow surfaces.

What is claimed is:

1. A package for use in a powder inhaler, the package being optimised in its shape and in the fill level to a pharmaceutical composition, mixture, or formulation and adapted to be opened in such a way that the delivery of the pharmaceutical composition, mixture, or formulation is optimised, wherein the package is a capsule or a blister, a blister disc, a blister coil, or a blister strip with one or more wells, and wherein, per capsule or well, the sum of the inflow surfaces is equal to the sum of the outflow surface or surfaces per well or capsule.

2. The package according to claim 1, wherein the package is a capsule.

3. The package according to claim 2, wherein the package is a size 2-4 capsule.

4. The package according to claim 2, wherein the package is a size 3 capsule.

5. The package according to claim 1, wherein the well or capsule is teardrop-shaped and the inflow surfaces and the outflow surface or surfaces are at the maximum spacing from one another.

6. The package according to claim 1, wherein the well or capsule is oval in shape and the inflow surfaces and the outflow surface or surfaces are at the maximum spacing from one another.

7. The package according to claim 1, wherein the well or capsule is in the form of a figure-of-eight and the inflow surfaces and the outflow surface or surfaces are at the maximum spacing from one another.

8. The package according to claim 1, wherein the well or capsule has a shape as shown in any one of FIGS. **1-13**.

9. The package according to claim 1, wherein the well or capsule has an opening pattern as shown in any one of FIGS. **1-13**.

10. A powder inhaler comprising a package that is optimised in its shape and in the fill level to a pharmaceutical composition, mixture, or formulation and adapted to be opened in such a way that the delivery of the pharmaceutical composition, mixture, or formulation is optimised, wherein the package is a capsule or a blister, a blister disc, a blister coil, or a blister strip with one or more wells, and wherein, per capsule or well, the sum of the inflow surfaces is equal to the sum of the outflow surface or surfaces per well or capsule.

11. The powder inhaler according to claim 10, wherein the package is a capsule.

12. The powder inhaler according to claim 11, wherein the package is a size 2-4 capsule.

13. The powder inhaler according to claim 11, wherein the package is a size 3 capsule.

14. The powder inhaler according to claim 10, wherein the well or capsule is teardrop-shaped and the inflow surfaces and the outflow surface or surfaces are at the maximum spacing from one another.

15. The powder inhaler according to claim 10, wherein the well or capsule is oval in shape and the inflow surfaces and the outflow surface or surfaces are at the maximum spacing from one another.

16. The powder inhaler according to claim 10, wherein the well or capsule is in the form of a figure-of-eight and the inflow surfaces and the outflow surface or surfaces are at the maximum spacing from one another.

17. The powder inhaler according to claim 10, wherein the well or capsule has a shape as shown in any one of FIGS. **1-13**.

18. The powder inhaler according to claim 10, wherein the well or capsule has an opening pattern as shown in any one of FIGS. **1-13**.

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