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(54) **ORODISPERSIBLE TABLETS CONTAINING FEXOFENADINE**

ORODISPERGIERBARE TABLETTEN MIT FEXOFENADIN

COMPRIMES ORODISPERSIBLES CONTENANT DU FEXOFENADINE

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- **SIMPSON K ET AL: "FEXOFENADINE A REVIEW OF ITS US IN THE MANAGEMENT OF SEASONAL ALLERGIC RHINITIS AND CHRONIC IDIOPATHIC URTICARIA" DRUGS, ADIS INTERNATIONAL LTD, AT, vol. 2, no. 59, February 2000 (2000-02), pages 301-321, XP001079065 ISSN: 0012-6667**

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Description

Field of the invention.

[0001] The present invention concerns orodispersible tablets comprising coated granules of fexofenadine. The invention also concerns said coated granules of fexofenadine, a process for the preparation thereof and the use of said orodispersible tablets.

[0002] In the context of the present invention, the term "orodispersible tablets" means tablets which are able to disintegrate in the buccal cavity in less than 60 seconds, preferably in less than 40 seconds, upon contact with saliva by formation of an easy-to-swallow suspension.

[0003] The disintegration time corresponds to the time between the moment when the tablet is placed in the buccal cavity in contact with saliva and the moment when the suspension (resulting from the disintegration without chewing of the tablet) is swallowed

Background of the invention.

[0004] Fexofenadine is a well known synthetic antiallergenic with the chemical name (±)-4-[1-hydroxy-4-[4(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethyl benzeneacetic acid.

[0005] Fexofenadine, a metabolite of terfenadine, is an antihistamine with selective peripheral H1-receptor antagonist activity.

[0006] Fexofenadine is known from e.g. US 4,254,129. It is acknowledged in the art and is commercially available, in particular as an oral tablet or capsule, under the trade name Allegra® .

[0007] The tablets, commercially available under the trade name Allegra® contain 30, 60, or 180 mg fexofenadine hydrochloride (depending on the dosage) and, as excipients, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and pregelatinized starch. Said tablets are coated with a film coating based on hydroxypropyl methylcellulose, mixture of iron oxides, polyethylene glycol, povidone, silicone dioxide, and titanium dioxide.

[0008] EP 1219291, which is a prior art according to Article 54(3) CBE, describes texture masked particles containing fexofenadine as active principle and a polymeric overcoating mixture made of cellulosic or acrylic polymers.

[0009] Fexofenadine is highly active via oral administration. While numerous pharmaceutical compositions for oral administration have been proposed, there still exists a need for commercially acceptable fexofenadine formulations for oral administration with good patient convenience and acceptance, especially for children or the elderly.

[0010] One particular difficulty in the formulation of fexofenadine in oral pharmaceutical compositions is its unpleasant, strong bitter taste and aftertaste.

[0011] Another difficulty in the formulation of fexofenadine in oral pharmaceutical compositions is the low solubility of fexofenadine, especially in gastric conditions (solubility of 0.2 mg of fexofenadine, HCl per ml of pH 1.2 aqueous buffer solution).

[0012] It is therefore highly desirable to develop coated granules, containing fexofenadine, which have taste-masking properties while permitting rapid release of the active substance from the granules and allowing rapid absorption in the body after oral administration.

[0013] Furthermore, some patients, especially children and the elderly, experience difficulties swallowing the tablets, even with liquids.

[0014] It is estimated that 50% of the population have problems swallowing the tablets. This leads to poor, or even noncompliance, with the treatment and thus has a negative impact on the efficiency of the treatment (H. Seager, 1998, J. Pharm. Pharmacol, 50, 375-382).

[0015] Oral disintegrable multiparticulate tablets have already been described in US 5,464,632, US 6,106,861, WO 00/27357 and WO00/51568. The active ingredient is in the form of coated microcrystals or coated microgranules.

[0016] Up to now, no oral formulations of fexofenadine exist which are specifically suitable for patients having difficulties when swallowing or for patients taking the drugs with no liquids.

[0017] It is thus highly desirable to remedy this situation and to develop an orodispersible tablet, containing fexofenadine, which has taste-masking properties and presents a pleasant palatability such that the administration of the tablet is not unpleasant for the patient and which allows the obtaining of pharmacokinetic parameters at least bioequivalent to those which are obtained with conventional oral formulations of fexofenadine, for example tablets such as those available under the trademark Allegra® .

[0018] The Applicant has now surprisingly found that these characteristics can be obtained by formulating a tablet containing fexofenadine as active ingredient in the form of coated granules, and a mixture of excipients containing at least one disintegrating agent, a soluble diluent agent and a lubricant, and optionally a swelling agent, an antistatic agent, a permeabilising agent, sweeteners, flavoring agents and colors.

[0019] The present invention relates to orodispersible tablets which are able to disintegrate in the buccal cavity upon

contact with saliva by formation of an easy-to-swallow suspension, in less than 60 seconds, preferably in less than 40 seconds, such tablets containing fexofenadine as active ingredient in the form of coated granules, and a mixture of excipients comprising at least one disintegrating agent, a soluble diluent agent, a lubricant and optionally a swelling agent, an antistatic agent, a permeabilising agent, sweeteners, flavoring agents and colors.

[0020] Surprisingly, although the tablets according to the invention disintegrate in the buccal cavity and present a release of the active ingredient which is equivalent to the conventional formulation, they nevertheless have a pleasant taste.

[0021] Furthermore, the orodispersible tablets of the invention are found to show high stability and physical integrity, e.g. during storage, handling, packaging and the like, while maintaining very good disintegration performance.

[0022] Fexofenadine may be used in the form of its racemate or a single enantiomer, in free base form or in acid addition salt form of the racemate or one of its single enantiomers. An acid addition salt form may be prepared from the free base form in a conventional manner and vice-versa. Examples of suitable acid addition salt forms include hydrochloride, lactate and ascorbate, preferably hydrochloride. Fexofenadine in the form of a hydrochloride salt is preferred.

[0023] In a preferred embodiment, fexofenadine particles present a particle size such that 100% of the particles have an average size of less than 20μm.

[0024] In the tablets according to the invention, fexofenadine in anyone of said forms is present as coated granules.

[0025] In the present patent application, the term "fexofenadine" is employed for designating anyone of its specific forms.

[0026] According to an advantageous embodiment, the tablet according to the invention, has a hardness of not less than 15 N, when measured with the test method of the European Pharmacopeia (2.9.8).

[0027] According to an advantageous embodiment, the tablet according to the invention contains coated granules of fexofenadine, or one of its pharmaceutically acceptable salts, and a mixture of excipients, the ratio of the mixture of excipients to the coated granules is 0.4 to 9, preferably 1.5 to 5 and even more preferably 2 to 3 parts by weight, the mixture of excipients comprising:

- at least one disintegrating agent,
- a soluble diluent agent,
- a lubricant,
- and optionally a permeabilising agent, a swelling agent, an antistatic agent, sweeteners, flavoring agents and colors.

[0028] The disintegrating agent is selected from the group consisting of croscarmellose, available as e.g. Ac-di-sol®, crospovidone available as e.g. Kollidon CL®, and mixtures thereof.

[0029] According to an advantageous embodiment of the invention, the soluble diluent agent used in the tablets presents binding properties. The soluble diluent agent with binding properties consists of a polyol having less than 13 carbon atoms and being either in the form of a directly compressible product with an average particle size of 100 to 500 μm, or in the form of a powder with an average particle size of less than 100 μm, this polyol, preferably being selected from the group comprising mannitol, xylitol, sorbitol and maltitol, it being understood that sorbitol cannot be used alone and that, in the case where there is only one soluble diluent agent with binding properties, it is used in the form of the directly compressible product, whereas in the case where there are at least two soluble diluent agents with binding properties, one is present in the directly compressible form and the other is present in powder form, it then being possible for the polyols to be the same, the ratio of directly compressible polyol to powder polyol being 99/1 to 20/80, preferably 80/20 to 20/80.

[0030] The proportion of disintegrating agent is from 3 to 15% by weight, preferably 5 to 15% by weight, in the case of a mixture, each disintegrating agent being comprised between 1 and 10% by weight, preferably 5 to 10 % by weight, and the proportion of soluble diluent agent being 30 to 90% by weight, preferably 40 to 60% by weight, based in each case on the weight of the tablet.

[0031] The lubricant is selected from the group consisting of magnesium stearate, stearic acid, sodium stearyl fumarate, micronised polyoxyethyleneglycol (micronised Macrogol 6000), leukine, sodium benzoate and mixtures thereof.

[0032] The amount of lubricant is from 0 to 3 %, preferably from 1 to 2 % by weight, based on the weight of the tablet.

[0033] The lubricant can be dispersed within the mixture of excipients, or according to an advantageous embodiment, sprayed over the outer surface of the tablet. Thus, according to an advantageous embodiment of the tablets of the invention, the lubricant is in powder form and is, at least in part, disposed on the surface of the tablets.

[0034] The permeabilising agent allows the creation of a hydrophilic network which facilitates the penetration of saliva and hence assists the disintegration of the tablet.

[0035] The permeabilising agent is selected from the group comprising especially silica with a high affinity for aqueous solvents, such as colloidal silica (Aerosil®), precipitated silica (Syloïd® FP 244), maltodextrins, β-cyclodextrins and mixtures thereof.

[0036] The amount of permeabilising agent is between 0 and 5%, preferably from 0.5 to 2% by weight, based on the

weight of the tablet.

[0037] A swelling agent can be incorporated in the mixture of excipients. Said swelling agent is selected from the group consisting of starch, modified starch or microcristalline cellulose.

[0038] An antistatic agent can be incorporated as a flow aid, said antistatic agent being selected from the group consisting of micronised or non micronised talc, fumed silica (Aerosil® R972), colloidal silica (Aerosil® 200), precipitated silica (Syloïd® FP 244), and mixtures thereof.

[0039] The sweetener which can be included in the mixture of excipients, can be selected from the group consisting of especially aspartam, potassium acesulfame, sodium saccharinate, neohesperidin dihydrochalcone, sucralose, monoammonium glycyrrhizinate, and mixtures thereof.

[0040] The flavorings and colors are those conventionally used in pharmacy for the preparation of tablets.

[0041] The present invention also relates to the coated granules of fexofenadine or one of its pharmaceutically acceptable salts.

[0042] The taste-masking of fexofenadine is achieved by coating granulated microcrystals of fexofenadine with one or more polymers.

[0043] According to an advantageous embodiment of the invention, the granules of fexofenadine, or one of its pharmaceutically acceptable salts, are characterized in that the granules are coated and that they contain:

- microcrystals of fexofenadine, or one of its pharmaceutically acceptable salts,
- at least one binder,
- optionally a diluent agent, an antistatic agent, a sweetening agent and/or a coloring agent.

[0044] Furthermore, the granulation excipients can also include disintegrating agents and/or surfactants.

[0045] The binder is selected from the group consisting of cellulosic polymers, such as ethylcellulose, hydroxypropylcellulose and hydroxypropylmethyl cellulose, acrylic polymers, such as insoluble acrylate ammoniomethacrylate copolymer, polyacrylate or polymethacrylic copolymer, povidones, copovidones, polyvinylalcohols, alginic acid, sodium alginate, starch, pregelatinized starch, sucrose and its derivatives, guar gum, polyethylene glycol, preferably an acrylic polymer, most preferably Eudragit® E100, and mixtures thereof.

[0046] Optionally, in order to enhance the granulation of the fexofenadine or one of its pharmaceutically acceptable salts, a diluent agent is used.

[0047] The diluent agent is selected from the group consisting of microcrystalline cellulose, sucrose, dicalcium phosphate, starches, lactose and polyols of less than 13 carbon atoms, such as mannitol, xylitol, sorbitol, maltitol, pharmaceutically acceptable aminoacids, such as glycin, and their mixtures.

[0048] The antistatic agent, which can be used as flow aid, is selected from the group consisting of micronised or non micronised talc, fumed silica (Aerosil® R972), colloidal silica (Aerosil® 200), precipitated silica (Syloïd® FP244) and mixtures thereof.

[0049] Conventional pharmaceutically acceptable sweetening agents and/or colouring agents can be incorporated into the granules of fexofenadine.

[0050] In a particular embodiment, the granule of fexofenadine or one of its pharmaceutically acceptable salts, is in the form of a core of granulated microcrystals of fexofenadine, coated with at least one layer comprising fexofenadine.

[0051] Said coated core is characterized in that the core and the layer comprise each from 70% to 95%, preferably 80% to 95% by weight of fexofenadine, or one of the pharmaceutically acceptable salts thereof, the balance to 100% being formed with at least one binder, and that said coated core is advantageously a sphere. Such a specific structure has previously been described by the Applicant in the French patent application FR 00 14803.

[0052] According to another embodiment of the invention, the granules comprise :

- from 10% to 95%, preferably from 50% to 70% of fexofenadine, or one of the pharmaceutically acceptable salts thereof,
- at most 20%, preferably at most 10% by weight of the binder, relative to the weight of fexofenadine, or one of the pharmaceutically acceptable salts thereof,
- at most 5%, preferably 2% by weight of the antistatic agent, relative to the weight of said granules
- optionally a diluent agent for the balance to 100%.

[0053] In order to ensure efficient taste masking, and a dissolution profile of the active substance such that more than 70% of the active substance is released in 30 minutes, preferably more than 90% is released in 30 minutes, the granules are coated with a coating composition containing at least one coating polymer selected from the group consisting of cellulosic polymers, acrylic polymers and their mixtures.

[0054] Among the cellulosic polymers, ethylcellulose, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC), are advantageously used.

[0055] Among the acrylic polymers, insoluble acrylate ammoniomethacrylate copolymer (Eudragit® RL100 or RS100 or Eudragit® RL30D or RS30D), polyacrylate (Eudragit® NE30D), or methacrylic copolymers (Eudragit® L100-55 or Eudragit® L30D, Eudragit® E100, Eudragit® EPO...) are advantageously used, alone, in combination or in admixture with pH-dependent polymers. Eudragit® E100 or a mixture of Eudragit® EPO and Eudragit® NE30D are preferred.

[0056] In a preferred embodiment, the binder and the coating polymer are the same polymer.

[0057] The prepared coating liquid is either water-based or prepared with organic solvents. According to an advantageous embodiment, this coating liquid is suitable to be sprayed with conventional spray layering equipment, as for example a fluidized bed equipped with a top insert-or-bottom (würster) insert.

[0058] Optionally permeabilising agents, plasticizers, soluble agents, disintegrating agents and surfactants are added as coating additives.

[0059] The plasticizer is selected in the group consisting of triacetine, triethylacetate, triethylcitrate (Eudraflex®), ethylphthalate, or mixtures thereof. The plasticizer is used in proportions of at most about 30%, preferably 10% by weight of the coating polymers.

[0060] The soluble agents are selected in particular among the polyols having less than 13 carbon atoms .

[0061] The disintegrating agent or a surfactant which could be added during the granulation and the coating steps allow improved dissolution.

[0062] The surfactant may be an anionic, nonionic, cationic or amphoteric surfactant.

[0063] The disintegrating agent is selected from the group consisting of croscarmellose, available as e.g. Ac-di-sol® , crospovidone available as e.g. Kollidon CL® , and mixtures thereof.

[0064] The particle size range of coated granules comprising fexofenadine, or one of its pharmaceutically acceptable salts is adapted for obtaining an effective taste masking with an acceptable coating factor and a good mouthfeel.

[0065] Advantageously the coated granules according to the invention have a particle size distribution between 150 μm and 500 μm, preferably between .150 μm and 425 μm, such that at least 50%, preferably at least 70% of the granules have a particle size ranging between 150, and 425μm and less than 15% of the granules have a particle size less than 150 μm. The particle sizes are measured according to conventional methods, preferably by sieving.

[0066] A granulation step is needed in order to obtain such particle size distribution.

[0067] In a particular embodiment, the coated granules according to the invention comprise:

- from 10% to 95%, preferably 40 to 75% of granules of fexofenadine, or one of its pharmaceutically acceptable salts, preferably fexofenadine HCl,
- from 5 to 90%, preferably 10 to 70% and even more preferably from 25 to 55% of a coating polymer, preferably Eudragit® E100, the percentages being expressed by weight relative to the weight of the granules of fexofenadine, or one of its pharmaceutically acceptable salts,
- from 0 to 10% of a permeabilising agent, preferably colloidal silica, the percentages being expressed by weight relative to the weight of the coating polymer.

[0068] Determination of workable proportions in any particular instance will generally be within the capability of the person skilled in the art. All indicated proportions and relative weight ranges described above are accordingly to be understood as being indicative of preferred or individually inventive teachings only.

[0069] Details concerning any of the excipients of the invention may be found in Fiedler, H. P. "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, 4th revised and expanded edition (1996); " Handbook of Pharmaceutical Excipients", 2nd Edition, Editors A. Wade and P. J. Weller (1994), Joint publication of American Pharmaceutical Association, Washington, USA and The Pharmaceutical Press, London, England; or may be obtained from the relevant manufacturers.

[0070] The invention also relates to a process for the preparation of coated granules of fexofenadine, which comprises the successive steps consisting in:

- dry mixing the microcrystals of fexofenadine or one of its pharmaceutically acceptable salts optionally with an antistatic agent and/or a diluent agent ;
- granulating the mixture obtained in the above step by spraying of a solution or suspension of at least one binder,
- optionally applying a layer over the thus obtained granules by spraying thereon a suspension, or a solution comprising fexofenadine, or one of its pharmaceutically acceptable salts with at least one binder,
- coating the thus obtained granules with a suspension of a coating composition,
- drying the thus obtained coated granules.

[0071] The invention also concerns a process for preparing orodispersible tablets comprising coated granules of fexofenadine, or one of its pharmaceutically acceptable salts.

[0072] The process comprises the successive steps consisting in :

- dry mixing the microcrystals of fexofenadine, or one of its pharmaceutically acceptable salts, optionally with an antistatic agent, a diluent agent, a permeabilising agent, a sweetening agent and/or a coloring agent;
- granulating the thus obtained mixture by spraying thereon a solution or a suspension of at least one binder,
- optionally applying a layer over the thus obtained granules by spraying thereon a suspension, or a solution comprising fexofenadine, or one of its pharmaceutically acceptable salts with at least one binder.
- coating the thus obtained granules by spraying thereon a suspension, a dispersion or a solution of the coating composition,
- drying the thus obtained coated granules,
- dry mixing coated granules and a mixture of excipients consisting of at least one disintegrating agent, a soluble diluent agent, and optionally a lubricant, a permeabilising agent, a swelling agent, sweeteners, an antistatic agent, flavorings and colors,
- compressing the mixture of coated granules and excipients into a tablet.

[0073] The lubricant can be mixed with the excipients for the tablet, but can advantageously be sprayed on the surface of the punches before tabletting.

[0074] In this process the mixing, granulating and coating steps can be performed in different or in the same equipment, each step being performed in the presence of a mixture of excipients which are identical or different.

[0075] For granulating, high shear mixer, planetary mixer or fluidized bed with insert used for bottom spray, granulation, tangential spray granulation, top spray granulation can be used, bottom spray granulation being preferred.

[0076] In an advantageous embodiment, each step is performed on a fluidized air-bed, such as for example, but not limited to Glatt GPCG-1, GPCG-3, GPCG-5 or GPCG 120.

[0077] For coating, bottom, top and tangential spray methods can be used as well as layering method, bottom spray method of coating being preferred.

[0078] For compressing the mixture of coated granules and excipients into a tablet, various punches may be used, with diameters comprised between 8 and 17 mm, depending upon the dosage of the tablet.

[0079] Various shapes may be used, such as for example, flat shape, advantageously with bevelled edges or polo punches.

[0080] The orodispersible tablets of the present invention show rapid disintegration in the buccal cavity upon contact with saliva without chewing, in less than 60 seconds, preferably in less than 40 seconds, have a pleasant taste and palatability and thus have particularly good patient convenience and patient acceptance due to their increased ease of administration and ingestion.

[0081] In addition the tablets of the invention show surprisingly high physical stability and are easy to handle and package.

[0082] According to a preferred embodiment, the tablet of the invention presents the following composition:

- granules of Fexofenadine HCl coated with Eudragit® E100,
- and a mixture of excipients consisting of Eudragit® E100, mannitol powder, mannitol granular, Crospovidone , precipitated silica, sweeteners and flavors.

[0083] For the preparation of said tablets, isopropanol is used as solvent and removed during the coating and granulation processes.

[0084] According to an advantageous embodiment, the tablet of the invention has the following composition:

<u>Fexofenadine coated granules</u>

[0085]

- Fexofenadine HCl : 40-80%
- Eudragit® E100 : 20 - 60%
- Precipitated silica : 0 - 5 %

the percentages being calculated by weight of coated granules,

<u>Excipients for the formulation of the tablet</u>

[0086]

- Fexofenadine coated granules 10-45%

- Mannitol powder and/or granular 50-90%
- Crospovidone 2 - 15 %
- Precipitated silica 0 - 5 %
- Magnesium stearate 0 - 5%
- Sucralose 0 - 5%
- Flavors 0 - 2 %

the percentages being calculated by weight of the tablet.

[0087] For the preparation of said tablets, isopropanol is used as solvent and removed during the coating and granulation processes.

[0088] The tablets are particularly effective in treating seasonal allergic rhinitis, in adults and children 6 years of age and older.

[0089] The present invention also concerns the use of a coated granules of fexofenadine with a mixture of excipients, as described above, for the manufacture of a medicament for the treatment of symptoms associated with seasonal allergic rhinitis.

[0090] The tablets of fexofenadine according to the invention are orally administered to the patients.

[0091] Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery, rhinitis.

[0092] The utility of the tablets of the present invention may be observed in standard bioavailability tests or standard animal models, for example ascertaining dosages of the present tablets giving blood levels of fexofenadine hydrochloride equivalent to blood levels having a therapeutical effect on administration of known fexofenadine oral dosage forms, e.g. a tablet.

[0093] The appropriate dosage will, of course, vary depending upon, for example, the host and the nature and severity of the condition being treated. However, in general satisfactory results in animals are indicated to be obtained by daily treatments. In humans an indicated daily dosage is in the range from about 10 mg to about 500mg per day, preferably from 30mg to 180mg, conveniently administered, for example, in divided doses up to four times a day or once daily. Preferred dosages, expressed as fexofenadine HCl, for children 6 to 11 years of age are about 30 mg two times a day, and for adults and children 12 years of age and older from about 60 mg two times a day, or 180 mg once a day.

[0094] The invention is illustrated more in detail in the following examples.

EXAMPLES

[0095] Particle size of Fexofenadine HCl used for the manufacture of granules of examples 1 to 4 is measured with conventional laser equipment.

[0096] Particle size distribution has following characteristics :

$D_{10\%}$	2.1 μm
$D_{50\%}$	5.3 μm
$D_{90\%}$	**11.1 μm**

In the examples below, the following excipients are used :

- Methacrylic polymer sold under tradename Eudragit® EPO or Eudragit® E100.
- Polyacrylate sold under the tradename Eudragit® NE30D.
- Mannitol powder
- Mannitol granular 300
- Sucralose
- Aspartam
- Peppermint, wildberry as flavoring agents
- Precipitated silica sold under the name Syloïd FP244
- Polyvinylpyrrolidone sold under the name PVP K90

[0097] Examples 1 to 4 relate to the preparation of coated granules of fexofenadine.

Example 1 :

Granulating step

[0098] 500 g of fexofenadine HCl mixed with 15 g of Syloïd FP 244 were granulated in a fluidized bed with 465 g of a mixture of Eudragit EPO/Eudragit NE30D (50/50) in water at 16 % (weight/weight):

Coating step:

[0099] The thus obtained granules were coated in a fluidized bed equipped with a top insert, by spraying thereon a dispersion of 465 g of a mixture of Eudragit EPO/Eudragit NE30D (50/50) in water at 16 % (weight/weight).
[0100] The amount of coating was of 12.5 % by weight with respect to the weight of the granules of fexofenadine HCl.
[0101] The dissolution rates of the thus obtained coated granules were measured with the following method :

- Apparatus : SP Apparatus II (Paddle method)
- Speed : 50 rpm
- Volume : 900 mL of HCl 0.001 N pH 3.0*
- Temperature : 37.0°C ±0.5°C
- Sampling (5 mL) : 2.5, 7.5, 15, 30 and 60 minutes
- HPLC Detection : UV at 220 nm
- HPLC column : Zorbax SB-Phenyl, 5 μm, 4.6 X 250 mm.
- Injection volume : 20 μL
- Mobile Phase : Acetonitrile: 0.03 M Acetic acid containing Triethylamine pH 5.25 (36:64).
- Dissolution medium : HCl 0.001 N adjusted to pH 3.0±0,05 (if necessary) with o-Phosphoric acid.

[0102] The results are given in the following table 1 :

Table 1

	Dissolved fexofenadine in %(w/w)
5 minutes	55 %
10 minutes	70 %
15 minutes	75 %
30 minutes	85 %

[0103] More than 80% of fexofenadine is dissolved after 30 minutes, taste-masking is efficient.

Example 2:

Granulating step

[0104] 500 g of fexofenadine HCl mixed with 15 g of Syloid FP244 were granulated in a fluidized bed with 30 g of an aqueous solution of PVP K90 at 8 % (weight/weight).

Coating step:

[0105] The thus obtained granules were coated in a fluidized bed equipped with a top insert, by spraying thereon a mixture of Eudragit EPO/Eudragit NE30D (60/40) in water at 16 % (weight/weight)
[0106] The amount of coating was of 40 % by weight with respect to the weight of the granules of fexofenadine HCl.
[0107] The particle size distribution (Sieve method) is given in the following table.

Table 2

Sieve operture	After Granulating step	After Coating step
>0.500mm	14.5%	5.7%

(continued)

Sieve operture	After Granulating step	After Coating step
0.425mm-0.500mm	13.0%	24.1 %
0.355mm-0.425mm	20.0%	9.5%
0.250mm-0.355mm	30.5%	28.9%
0.150mm-0.250mm	21.5%	31.5%
<0.150mm	0.5%	0.3%

[0108] The dissolution rates of said granules were measured as indicated in example 1 above.
[0109] The results are given in the following table 3:

Table 3

	Dissolved fexofenadine in %(w/w)
5 minutes	65 %
10 minutes	85 %
15 minutes	100%
30 minutes	100 %

[0110] More than 80% of fexofenadine is dissolved after 30 minutes, taste-masking is efficient.

Example 3 :

Granulating step

[0111] 1000 g of fexofenadine HCl mixed with 30 g of Syloïd FP 244 were granulated in a fluidized bed equipped with a Wurster insert with 1 500 g of an solution of Eudragit E100 in isopropanol at 12 % (weight/weight).

Coating step:

[0112] The thus obtained granules were coated in a fluidized bed equipped with a top insert, by spraying thereon a polymeric dispersion of 3 900g of Eudragit E100 in isopropanol at 12% (weight/weight) containing 1 % of Syloïd FP 244.
[0113] The amount of coating was of 38% by weight with respect to the weight of the granules of fexofenadine HCl.
[0114] The particle size distribution (Sieve method) is given in the following table.

Table 4

Sieve operture	Coated granules
>0.600mm	0 %
0.500mm-0.600mm	1.0%
0.425mm-0.500mm	9.2%
0.355mm-0.425mm	18.6%
0.250mm-0.355mm	36.2%
0.150mm-0.250mm	30.2%
0.090mm-0.150mm	3.4%
<0.090mm	1.4%

[0115] The dissolution rates of said granules were measured as indicated in example 1 above.
[0116] The results are given in the following table 5.:

Table 5

	Dissolved fexofenadine in %(w/w)
5 minutes	55 %
10 minutes	85 %
15 minutes	95 %
30 minutes	100%

[0117] More than 80% of fexofenadine is dissolved after 30 minutes, taste-masking is efficient.

Example 4 :

Granulating step

[0118] 1000 g of fexofenadine HCl mixed with 30 g of Syloid FP 244 were granulated in a planetary mixer with 400 g of an solution of Eudragit E100 in isopropanol at 12 % (weight/weight).

Coating step:

[0119] The obtained granules were coated in a fluidized bed equipped with a Wurster insert, by spraying thereon a solution of Eudragit E100 in isopropanol at 10 % (weight/weight) containing 1 % of Syloïd FP 244.
[0120] The amount of coating was of 30% by weight with respect to the weight of the granules of fexofenadine HCl.
[0121] The dissolution rates of said granules were measured as indicated in example 1 above.
[0122] The results are given in the following table 6:

Table 6

	Dissolved fexofenadine in %(w/w)
5 minutes	40 %
10 minutes	80 %
15 minutes	95 %
30 minutes	100 %

[0123] 100% of fexofenadine is dissolved after 30 minutes, taste-masking is efficient.
[0124] Examples 5-8 relate to the preparation of tablets.

Example 5 :

[0125] Three types of tablets T1, T2, T3 were prepared using coated granules of fexofenadine presenting different coating ratios. The coated granules of fexofenadine were obtained as in example 3 above but using the three different coating ratios of 30, 35 and 40. Then, an amount of each type of said coated granules corresponding to 180 mg of fexofenadine HCl was thoroughly blended for 15 minutes with the following tablet excipients.

Crospovidone	10%
Silica	0.5%
Magnesium stearate	0.5%
Aspartame	2%
Flavor	1 %.
Mannitol powder (60 μm) /granular (330 μm) (2/1)	qs 100%

[0126] The percentages are expressed as percentage of the total weight of a tablet.
[0127] The homogeneous obtained blend was introduced in a tabletting machine equipped with14 mm-diameter polo

shape punches.

[0128] These tablets T1, T2 and T3 were obtained.

[0129] For each tablet thus obtained, the weight, hardness, disintegrating time in mouth, mouthfeel and taste were measured.

[0130] The results are displayed in the table 7

Table 7

Tablets	T1	T2	T3
Coated granule ratio (% by weight)	30	35	40
Weight	920 mg	780 mg	690 mg
Hardness	44 N	39 N	45 N
Disintegration time in mouth	15-20 sec.	15-20 sec	20-25 sec.
Mouthfeel	Complies	Complies	Complies
Taste	Complies	Complies	Complies

[0131] T1, T2, T3 present an acceptable dissolution rate with good taste and pleasant mouthfeel and disintegrate in buccal cavity in less than 30 seconds.

Example 6

[0132] As in example 5, three types of tablets (T4, T5, T6) presenting coated granules of fexofenadine with coating ratios of 30, 35, 40 were prepared but using an amount of fexofenadine HCl equivalent to 30 mg per tablet.

[0133] The homogeneous obtained blend was introduced in a tabletting machine equipped with polo shape punches as described in the table.

[0134] Results are displayed in the table 8

Table 8

Tablets	T4	T5	T6
Coated granule ratio (% by weight)	30	35	40
Punch diameter	8 mm	7 mm	6 mm
Weight	153 mg	131 mg	115 mg
Hardness	44 N	39 N	45 N
Disintegration time in mouth	15-20 sec.	15-20 sec	20-25 sec.
Mouthfeel	Complies	Complies	Complies
Taste	Complies	Complies	Complies

[0135] Tablets T4, T5 and T6 present an acceptable taste and pleasant mouthfeel and disintegrate in buccal cavity in less than 30 seconds.

Example 7

[0136] Tablets T7 according to the formula of T2 of example 5 are manufactured, using a ratio of Mannitol powder/ Mannitol granular ratio of 1/1, containing an amount of fexofenadine HCl equivalent to 180 mg per tablet..

[0137] The homogeneous obtained blend was introduced in a tabletting machine equipped with 14 mm-diameter polo shape punches.

[0138] The disintegration time in the mouth, the mouthfeel and taste were evaluated.

[0139] The results are displayed in the table 9.

Table 9

Tablets	T7
Disintegration time in mouth	25 sec.
Mouthfeel	Complies
Taste	Complies

[0140] Tablets T7 with a mannitol powder/granular ratio of 1/1 (w/w) present a good taste and pleasant mouthfeel and disintegrate in buccal cavity in less than 30 seconds.

Example 8

[0141] Three types of tablets (T8, T9, T10) according to the formula T2 of example 5 were manufactured but using three different ratios of crospovidone of 5, 7.5 and 10% by weight.

[0142] The homogeneous obtained blend was introduced in a tabletting machine equipped with 14mm-diameter polo shape.

[0143] Tablets T8, T9 and T10 were thus obtained. The disintegrating time in mouth, the hardness, the mouthfeell and taste were evaluated, the results are displayed in table 10.

Table 10

Tablets	T8	T9	T10
Crospovidone ratio (% by weight)	5	7.5	10
Hardness	44 N	45 N	45 N
Disintegration time in mouth	20-25 sec.	20-25 sec	20-25 sec.
Mouthfeel	Complies	Complies	Complies
Taste	Complies	Complies	Complies

[0144] Tablets T8, T9 and T10 present an acceptable taste and pleasant mouthfeel and disintegrate in buccal cavity in less than 30 seconds.

Exemple 9 : Pharmacokinetic studies

[0145] A bioequivalence study was conducted with two tablets (T11 and T12) according to the invention versus Allegra® 180 mg (Reference).

[0146] 15 subjects received T11 versus Reference and 13 subjects received T12, each versus Reference

[0147] The respective compositions of T11 and T12 are given below :

	T11	T12
Fexofenadine HCl coated granules		
Fexofenadine HCl	48.4%	58.2%
Eudragit E100	48.4%	37.7%
Silica	4.2%	4.1 %

Tablets	
Coated granules corresponding to 180mg of Fexofenadine HCl	30%
Crospovidone	5%
Silica	0.5%
Magnesium stearate	1 %
Sucralose	2%
Flavor	0,2%
Mannitol powder(60 μm) /granular (330 μm) (1/1)	qs 100%

Said tablets were prepared according to the process of example 5 above. The tablets (Prototype and Reference) were administered to fasting patients. Pharmacokinetic parameters obtained for each prototype A and B and Reference are listed in tables 11 and 12 :

Table 11

Test 1 (n=15) - mean values	AUC (CV)	Cmax (CV)	Tmax (CV)
Reference	3132,2	453,8	2,0
T11 (% as exp. versus reference)	3804,4 (121)	571,2 (126)	2,9 (144)

[0148] T11 under fasting conditions has slightly higher bioavailability relative to the reference.

Table 12

Test 2 (n=13) - mean values	AUC	Cmax	Tmax
Reference	3017,0	457,3	2,2
T12 (% as exp. versus reference)	3047,1 (101)	409,8 (90)	2,6 (115)

[0149] T12 under fasting is bioequivalent relative to the reference tablet.

Claims

1. Orodispersible tablets, which are able to disintegrate in the buccal cavity upon contact with saliva by formation of an easy-to-swallow suspension, in less than 60 seconds containing:

(i) fexofenadine, or at least one of its pharmaceutically acceptable salt, in the form of coated granules, and
(ii) a mixture of excipients comprising at least one disintegrating agent, a soluble diluent agent, a lubricant.

2. Orodispersible tablets according to claim 1, which are able to disintegrate in less than 40 seconds.

3. Orodispersible tablets according to claim 1, wherein the mixture of excipients further comprises a swelling agent, an antistatic agent, a permeabilising agent, sweeteners, flavoring agents or colors.

4. Orodispersible tablets according to claim 1, wherein the weight ratio of the mixture of excipients to the coated granules is 0.4 to 9.

5. Orodispersible tablets according to claim 4, wherein the weight ratio of the mixture of excipients to the coated granules is 1.5 to 5.

6. Orodispersible tablets according to claim 5, wherein the weight ratio of the mixture of excipients to the coated granules is 2 to 3.

7. Orodispersible tablets according to claim 1, wherein the disintegrating agent is selected from the group consisting of croscarmellose, crospovidone, and mixtures thereof.

8. Orodispersible tablets according to claim 1, wherein the soluble diluent agent has binding properties and consists of a polyol having less than 13 carbon atoms and being either in the form of the directly compressible product with an average particle size of 100 to 500 μm, or in the form of a powder with an average particle size of less than 100 μm, this polyol preferably being selected from the group comprising mannitol, xylitol, sorbitol and maltitol, it being understood that sorbitol cannot be used alone and that, in the case where there is only one soluble diluent agent with binding properties, it is used in the form of the directly compressible product, whereas in the case where there are at least two soluble diluent agents with binding properties, one is present in the directly compressible form and the other is present in powder form, it then being possible for the polyols to be the same, the ratio of directly

compressible polyol to powder polyol being 99/1 to 20/80, preferably 80/20 to 20/80.

9. Orodispersible tablets according to claim 1, wherein the proportion of disintegrating agent is from 3 to 15% by weight, and the proportion of soluble diluent agent is 30 to 90% by weight, the percentages being based on the weight of the tablet.

10. Orodispersible tablets according to claim 9, wherein the proportion of disintegrating agent is from 5 to 15% by weight, and the proportion of soluble diluent agent is from 40 to 60% by weight, the percentages being based on the weight of the tablet.

11. Orodispersible tablets according to claim 1, wherein the lubricant is selected from the group consisting of magnesium stearate, stearic acid, sodium stearyl fumarate, micronised polyoxyethyleneglycol, leukine, sodium benzoate and mixtures thereof.

12. Orodispersible tablets according to claim 3, wherein the sweetener is selected from the group consisting of aspartam, potassium acesulfame, sodium saccharinate, neohesperidin dihydrochalcone, sucralose, monoammonium glycyrrhizinate, and mixtures thereof.

13. Orodispersible tablets according to claim 11, wherein the lubricant is in powder form and is, at least in part, disposed on the surface of the tablets.

14. Granules of fexofenadine, or one of its pharmaceutically acceptable salts, wherein the granules are coated and contain:

- microcrystals of fexofenadine, or one of its pharmaceutically acceptable salts,
- at least one binder selected from the group consisting of cellulosic polymers, such as ethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, acrylic polymers such as insoluble acrylate ammoniomethacrylate copolymer, polyacrylate or polymethacrylic copolymer, povidones, copovidones, polyvinylalcohols, alginic acid, sodium alginate, starch, pregelatinized starch, sucrose and its derivatives, guar gum, polyethylene glycol and mixtures thereof.

15. Granules according to claim 14 which further contain a diluent agent selected from the group consisting of microcrystalline cellulose, sucrose, dicalcium phosphate, starches, lactose, polyols of less than 13 carbon atoms such as mannitol, xylitol, sorbitol, maltitol, pharmaceutically acceptable aminoacids such as glycin, and their mixtures, an antistatic agent selected from the group consisting of micronised or non micronised talc, fumed silica, precipitated and colloidal silica, a sweetening agent or a coloring agent.

16. Granules according to claim 14, which further comprise a desintegrating agent selected from the group consisting of croscarmellose, crospovidone and mixtures thereof or a surfactant which can be an anionic, nonionic, cationic or amphoteric surfactant.

17. Granules according to claim 15, comprising:

- from 10% to 95% of fexofenadine, or one of the pharmaceutically acceptable salts thereof,
- at most 20% by weight of the binder, relative to the weight of fexofenadine, or one of the pharmaceutically acceptable salts thereof,
- at most 5% of the antistatic agent, relative to the weight of said granules.

18. Granules according to claim 17, comprising:

- from 50% to 70% of fexofenadine, or one of the pharmaceutically acceptable salts thereof,
- at most 10% by weight of the binder, relative to the weight of fexofenadine, or one of the pharmaceutically acceptable salts thereof,
- at most 2% by weight of the antistatic agent, relative to the weight of said granules.

19. Granules according to claim 17, further comprising a diluent agent for the balance to 100%.

20. Granules according to claim 18, further comprising a diluent agent for the balance to 100%.

21. Granules according to claim 14, wherein they are coated with a coating composition containing at least one coating polymer selected from the group consisting of cellulosic polymers such as ethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, acrylic polymers such as insoluble acrylate amoniomethacrylate copolymer, polyacrylate or methacrylic copolymers, and mixtures thereof.

22. Granules according to claims 21, wherein the coating composition further contains permeabilizing agents, plasticizers, soluble agents, desintegrating agents or surfactants.

23. Granules according to claim 22 comprising:

- from 10% to 95% of granules of fexofenadine, or one of its pharmaceutically acceptable salts,
- from 5 to 90% of a coating polymer, the percentages being expressed by weight relative to the weight of the granules of the fexofenadine, or one of its pharmaceutically acceptable salts,
- from 0 to 10% of a permeabilising agent, the percentages being expressed by weight relative to the weight of the coating polymer.

24. Granules according to claim 23 comprising :

- from 40 to 75% of granules of fexofenadine, or one of its pharmaceutically acceptable salts,
- from 10 to 70% of a coating polymer, the percentages being expressed by weight relative to the weight of the granules of the fexofenadine, or one of its pharmaceutically acceptable salts,
- from 0 to 10% of colloidal silica as permeabilising agent, the percentages being expressed by weight relative to the weight of the coating polymer.

25. granules according to claim 24, comprising from 25 to 55% of a coating polymer.

26. Granules according to claim 23, comprising fexofenadine hydrochloride.

27. Coated granules of fexofenadine, or one of its pharmaceutically acceptable salts, according to claim 14, which are coated with a coating layer containing fexofenadine wherein the granules and the coating layer comprise each from 70% to 95% by weight of fexofenadine, or one of the pharmaceutically acceptable salts thereof, the balance to 100% being formed with at least one binder.

28. Coated granules of fexofenadine, or one of its pharmaceutically acceptable salts, according to claim 27, which are coated with a coating layer containing fexofenadine wherein the granules and the coating layer comprise each from 80% to 95% by weight of fexofenadine, or one of the pharmaceutically acceptable salts thereof, the balance to 100% being formed with at least one binder.

29. Process for the preparation of granules according to claim 14 wherein it comprises the successive steps consisting in:

- dry mixing the microcrystals of the fexofenadine or one of its pharmaceutically acceptable salts;
- granulating the mixture obtained in the above step by spraying of a solution or suspension of at least one binder,
- coating the thus obtained granules with a suspension of a coating composition,
- drying the thus obtained coated granules.

30. Process for the preparation of granules according to claim 15, wherein it comprises the successive steps consisting in:

- dry mixing the microcrystals of the fexofenadine or one of its pharmaceutically acceptable salts with an antistatic agent or a diluent agent;
- granulating the mixture obtained in the above step by spraying of a solution or suspension of at least one binder,
- coating the thus obtained granules with a suspension of a coating composition,
- drying the thus obtained coated granules.

31. Process for the preparation of granules according to claim 27 wherein it comprises the successive steps consisting in:

- dry mixing the microcrystals of the fexofenadine or one of its pharmaceutically acceptable salts;
- granulating the mixture obtained in the above step by spraying of a solution or suspension of at least one binder,
- applying a layer over the thus obtained granules by spraying thereon a suspension, or a solution comprising

fexofenadine, or one of its pharmaceutically acceptable salts with at least one binder,
- coating the thus obtained granules with a suspension of a coating composition,
- drying the thus obtained coated granules.

32. Process according to claim 31 wherein it comprises the successive steps consisting in:

- dry mixing the microcrystals of the fexofenadine or one of its pharmaceutically acceptable salts with an antistatic agent or a diluent agent;
- granulating the mixture obtained in the above step by spraying of a solution or suspension of at least one binder,
- applying a layer over the thus obtained granules by spraying thereon a suspension, or a solution comprising fexofenadine, or one of its pharmaceutically acceptable salts with at least one binder,
- coating the thus obtained granules with a suspension of a coating composition,
- drying the thus obtained coated granules.

33. Process for the preparation of tablets according to claim 1, comprising the successive steps of :

- preparing coated granules of fexofenadine, or one of its pharmaceutically acceptable salts,
- dry mixing coated granules and a mixture of excipients comprising at least one disintegrating agent and a soluble diluent agent,
- compressing the mixture of coated granules and excipients into a tablet.

34. Process for the preparation of tablets according to claim 33, wherein the mixture of excipients further comprises a lubricant, a permeabilising agent, a swelling agent, sweeteners, an antistatic agent, flavorings and colors.

35. Use of a composition containing

(i) fexofenadine, or at least one of its pharmaceutically acceptable salt, in the form of coated granules, and
(ii) a mixture of recipients comprising at least one disintegrating agent, a soluble diluent agent, a lubricant,

for the manufacture of an orodispersible tablet according to claim 1, to be orally administered to patients suffering from symptoms associated with seasonal allergic rhinitis.

Patentansprüche

1. Orodispergierbare Tabletten, die in der Bukkalhöhle bei Kontakt mit Speichel durch Bildung einer leicht zu schluckenden Suspension in weniger als 60 Sekunden desintegrieren können, enthaltend:

(i) Fexofenadin oder mindestens ein pharmazeutisch annehmbares Salz davon in Form von beschichteten Körnern und
(ii) eine Mischung von Exzipienten, umfassend mindestens ein Desintegrationsmittel, ein lösliches Verdünnungsmittel, ein Gleitmittel.

2. Orodispergierbare Tabletten gemäß Anspruch 1, die in weniger als 40 Sekunden desintegrieren können.

3. Orodispergierbare Tabletten gemäß Anspruch 1, wobei die Mischung von Exzipienten weiterhin ein Schwellmittel, ein Antistatikum, ein Permeabilisierungsmittel, Süßmittel, Geschmacksmittel oder Farbstoffe umfaßt.

4. Orodispergierbare Tabletten gemäß Anspruch 1, wobei das Gewichtsverhältnis der Mischung von Exzipienten zu den beschichteten Körnern 0,4 bis 9 beträgt.

5. Orodispergierbare Tabletten gemäß Anspruch 4, wobei das Gewichtsverhältnis der Mischung von Exzipienten zu den beschichteten Körnern 1,5 bis 5 beträgt.

6. Orodispergierbare Tabletten gemäß Anspruch 5, wobei das Gewichtsverhältnis der Mischung von Exzipienten zu den beschichteten Körnern 2 bis 3 beträgt.

7. Orodispergierbare Tabletten gemäß Anspruch 1, wobei das Desintegrationsmittel ausgewählt ist aus der Gruppe

bestehend aus Croscarmellose, Crospovidon und Mischungen davon.

8. Orodispergierbare Tabletten gemäß Anspruch 1, wobei das lösliche Verdünnungsmittel Bindungseigenschaften aufweist und aus einem Polyol mit weniger als 13 Kohlenstoffatomen besteht und sich entweder in Form von einem direkt komprimierbaren Produkt mit einer durchschnittlichen Teilchengröße von 100 bis 500 μm oder in Form eines Pulvers mit einer durchschnittlichen Teilchengröße von weniger als 100 μm befindet, wobei dieses Polyol vorzugsweise ausgewählt ist aus der Gruppe umfassend Mannit, Xylit, Sorbit und Maltitol, wobei verstanden wird, daß Sorbit nicht allein verwendet werden kann und daß in dem Fall, in dem es nur ein lösliches Verdünnungsmittel mit Bindungseigenschaften gibt, es in Form eines direkt komprimierbaren Produkts verwendet wird, während in dem Fall, in dem es mindestens zwei lösliche Verdünnungsmittel mit Bindungseigenschaften gibt, eines in direkt komprimierbarer Form und das andere in Pulverform vorliegt, wodurch es dann möglich ist, daß die Polyole dieselben sind, wobei das Verhältnis von direkt komprimierbarem Polyol zu pulverförmigem Polyol 99/1 bis 20/80, vorzugsweise 80/20 bis 20/80 beträgt.

9. Orodispergierbare Tabletten gemäß Anspruch 1, wobei der Anteil des Desintegrationsmittels 3 bis 15 Gew.% und der Anteil des löslichen Verdünnungsmittels 30 bis 90 Gew.% ausmacht, wobei die Prozentsätze auf dem Gewicht der Tablette basieren.

10. Orodispergierbare Tabletten gemäß Anspruch 9, wobei der Anteil des Desintegrationsmittels 5 bis 15 Gew.% und der Anteil des löslichen Verdünnungsmittels 40 bis 60 Gew.% ausmacht, wobei die Prozentsätze auf dem Gewicht der Tablette basieren.

11. Orodispergierbare Tabletten gemäß Anspruch 1, wobei das Gleitmittel ausgewählt ist aus der Gruppe bestehend aus Magnesiumstearat, Stearinsäure, Natriumstearylfumarat, mikronisiertem Polyoxyethylenglycol, Leukin, Natriumbenzoat und Mischungen daraus.

12. Orodispergierbare Tabletten gemäß Anspruch 3, wobei das Süßmittel ausgewählt ist aus der Gruppe bestehend aus Aspartam, Kaliumacesulfam, Natriumsaccharinat, Neohesperidindihydrochalcon, Sucralose, Monoammoniumglycyrrhizinat und Mischungen daraus.

13. Orodispergierbare Tabletten gemäß Anspruch 11, wobei das Gleitmittel in Pulverform vorliegt und mindestens teilweise auf der Oberfläche der Tabletten angeordnet ist.

14. Körner von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze, wobei die Körner beschichtet sind und folgendes enthalten:

Mikrokristalle von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze,
mindestens ein Bindemittel, ausgewählt aus der Gruppe bestehend aus cellulosischen Polymeren wie z.B. Ethylcellulose, Hydroxypropylcellulose und Hydroxypropylmethylcellulose, Acrylpolymeren wie z.B. unlöslichem Acrylatammoniomethacrylat-Copolymer, Polyacrylat oder Polymethacryl-Copolymer, Povidonen, Copovidonen, Polyvinylalkoholen, Alginsäure, Natriumalginat, Stärke, prägelatinierte Stärke, Saccharose und ihren Derivaten, Guargummi, Polyethylenglycol und Mischungen davon.

15. Körner gemäß Anspruch 14, die weiterhin ein Verdünnungsmittel enthalten, ausgewählt aus der Gruppe bestehend aus mikrokristalliner Cellulose, Saccharose, Dicalciumphosphat, Stärken, Lactose, Polyolen mit weniger als 13 Kohlenstoffatomen wie z.B. Mannit, Xylit, Sorbit, Maltitol, pharmazeutisch annehmbaren Aminosäuren wie z.B. Glycin, und ihren Mischungen, einem antistatischen Mittel ausgewählt aus der Gruppe bestehend aus mikronisiertem oder nicht-mikronisiertem Talk, Quarzstaub, ausgefälltem und kolloidalem Siliziumdioxid, einem Süßmittel oder einem Färbemittel.

16. Körner gemäß Anspruch 14, die weiterhin ein Desintregrationsmittel umfassen, ausgewählt aus der Gruppe bestehend aus Croscarmellose, Crospovidon und Mischungen daraus, oder ein Tensid, das ein anionisches, nicht-ionisches, kationisches oder amphoteres Tensid sein kann.

17. Körner gemäß Anspruch 15, umfassend:

10 bis 95 % Fexofenadin oder eines der pharmazeutisch annehmbaren Salze davon,
höchstens 20 Gew.% Bindemittel relativ zum Gewicht von Fexofenadin oder einem seiner pharmazeutisch

annehmbaren Salze,
höchstens 5 % antistatisches Mittel relativ zum Gewicht der Körner.

18. Körner gemäß Anspruch 17, umfassend:

50 bis 70 % Fexofenadin oder eines der pharmazeutisch annehmbaren Salze davon,
höchstens 10 Gew.% Bindemittel relativ zum Gewicht von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze,
höchstens 2 % antistatisches Mittel relativ zum Gewicht der Körner.

19. Körner gemäß Anspruch 17, weiterhin umfassend ein Verdünnungsmittel für eine Balance auf 100 %.

20. Körner gemäß Anspruch 18, weiterhin umfassend ein Verdünnungsmittel für eine Balance auf 100 %.

21. Körner gemäß Anspruch 14, wobei sie mit einer Beschichtungszusammensetzung beschichtet sind, enthaltend mindestens ein Beschichtungspolymer, ausgewählt aus der Gruppe bestehend aus cellulosischen Polymeren wie z.B. Ethylcellulose; Hydroxypropylcellulose und Hydroxypropylmethylcellulose, Acrylpolymeren wie z.B. unlöslichem Acrylatammoniomethacrylat-Copolymer, Polyacrylat oder Methacryl-Copolymeren, und Mischungen daraus.

22. Körner gemäß Anspruch 21, wobei die Beschichtungszusammensetzung weiterhin permeabilisierende Mittel, Weichmacher, lösliche Mittel, Desintegrationsmittel oder Tenside enthält.

23. Körner gemäß Anspruch 22, umfassend:

10 bis 95 % Körner von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze,
5 bis 90 % eines Beschichtungspolymers, wobei die Prozentsätze durch Gewicht relativ zum Gewicht der Körner von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze ausgedrückt werden,
0 bis 10 % permeabilisierendes Mittel, wobei die Prozentsätze als Gewicht relativ zum Gewicht des Beschichtungspolymers ausgedrückt werden.

24. Körner gemäß Anspruch 23, umfassend:

40 bis 75 % Körner von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze,
10 bis 70 % eines Beschichtungspolymers, wobei die Prozentsätze durch Gewicht relativ zum Gewicht der Körner von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze ausgedrückt werden,
0 bis 10 % kolloidales Siliziumdioxid als permeabilisierendes Mittel, wobei die Prozentsätze als Gewicht relativ zum Gewicht des Beschichtungspolymers ausgedrückt werden.

25. Körner gemäß Anspruch 24, umfassend 25 bis 55 % eines Beschichtungspolymers.

26. Körner gemäß Anspruch 23, umfassend Fexofenadinhydrochlorid.

27. Beschichtete Körner von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze gemäß Anspruch 14, die mit einer Beschichtung enthaltend Fexofenadin beschichtet sind, wobei die Körner und die Beschichtungsschicht jeweils 70 bis 95 Gew.% Fexofenadin oder eines seiner pharmazeutisch annehmbaren Salze umfassen, wobei die Balance auf 100 % durch mindestens ein Bindemittel gebildet wird.

28. Beschichtete Körner von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze gemäß Anspruch 27, die mit einer Beschichtung enthaltend Fexofenadin beschichtet sind, wobei die Körner und die Beschichtungsschicht jeweils 80 bis 95 Gew.% Fexofenadin oder eines seiner pharmazeutisch annehmbaren Salze umfassen, wobei die Balance auf 100 % durch mindestens ein Bindemittel gebildet wird.

29. Verfahren zur Herstellung von Körnern gemäß Anspruch 14, wobei dieses die aufeinanderfolgenden Schritte umfaßt, bestehend aus:

Trockenmischen der Mikrokristalle von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze,
Granulieren der in dem obigen Schritt erhaltenen Mischung durch Versprühen einer Lösung oder Suspension von mindestens einem Bindemittel,

Beschichten der so erhaltenen Körner mit einer Suspension einer Beschichtungszusammensetzung,
Trocknen der so erhaltenen beschichteten Körner.

30. Verfahren für die Herstellung von Körnern gemäß Anspruch 15, wobei dieses die aufeinanderfolgenden Schritte umfaßt, bestehend aus:

Trockenmischen der Mikrokristalle von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze mit einem antistatischen Mittel oder einem Verdünnungsmittel, Granulieren der in dem obigen Schritt erhaltenen Mischung durch Versprühen einer Lösung oder Suspension von mindestens einem Bindemittel,
Beschichten der so erhaltenen Körner mit einer Suspension einer Beschichtungszusammensetzung,
Trocknen der so erhaltenen beschichteten Körner.

31. Verfahren für die Herstellung von Körnern gemäß Anspruch 27, wobei dieses die aufeinanderfolgenden Schritte umfaßt, bestehend aus:

Trockenmischen der Mikrokristalle von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze,
Granulieren der in dem obigen Schritt erhaltenen Mischung durch Versprühen einer Lösung oder Suspension von mindestens einem Bindemittel,
Aufbringen einer Schicht über die so erhaltenen Körner durch Versprühen einer Suspension oder einer Lösung, umfassend Fexofenadin oder eines seiner pharmazeutisch annehmbaren Salze mit mindestens einem Bindemittel darauf,
Beschichten der so erhaltenen Körner mit einer Suspension einer Beschichtungszusammensetzung,
Trocknen der so erhaltenen beschichteten Körner.

32. Verfahren gemäß Anspruch 31, wobei dieses die aufeinanderfolgenden Schritte umfaßt, bestehend aus:

Trockenmischen der Mikrokristalle von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze mit einem antistatischen Mittel oder einem Verdünnungsmittel, Granulieren der in dem obigen Schritt erhaltenen Mischung durch Versprühen einer Lösung oder Suspension von mindestens einem Bindemittel,
Aufbringen einer Schicht über die so erhaltenen Körner durch Versprühen einer Suspension oder einer Lösung, umfassend Fexofenadin oder eines seiner pharmazeutisch annehmbaren Salze mit mindestens einem Bindemittel darauf,
Beschichten der so erhaltenen Körner mit einer Suspension einer Beschichtungszusammensetzung,
Trocknen der so erhaltenen beschichteten Körner.

33. Verfahren für die Herstellung von Tabletten gemäß Anspruch 1, umfassend die aufeinanderfolgenden Schritte:

Herstellung von beschichteten Körnern von Fexofenadin oder einem seiner pharmazeutisch annehmbaren Salze,
Trockenmischen der beschichteten Körner und einer Mischung von Exzipienten, umfassend mindestens ein Desintregrationsmittel und ein lösliches Verdünnungsmittel,
Komprimieren der Mischung der beschichteten Körner und Exzipienten in eine Tablette.

34. Verfahren für die Herstellung von Tabletten gemäß Anspruch 33, wobei die Mischung von Exzipienten weiterhin ein Gleitmittel, ein Permeabilisierungsmittel, ein Schwellmittel, Süßmittel, ein Antistatikum, Geschmacksstoffe und Farbstoffe umfaßt.

35. Verwendung einer Zusammensetzung, enthaltend

(i) Fexofenadin oder mindestens eines seiner pharmazeutisch annehmbaren Salze in Form von beschichteten Körnern und
(ii) eine Mischung von Exzipienten, umfassend mindestens ein Desintegrationsmittel, ein lösliches Verdünnungsmittel, ein Gleitmittel zur Herstellung einer orodispergierbaren Tablette gemäß Anspruch 1, um oral an Patienten verabreicht zu werden, die an Symptomen leiden, die mit einer saisonalen allergischen Rhinitis assoziiert sind.

Revendications

1. Comprimés orodispersibles qui sont aptes à se désintégrer dans la cavité buccale au contact de la salive en formant une suspension aisé à avaler en moins de 60 secondes, contenant :

   (i) de la fexofenadine, ou l'un de ses sels pharmaceutiquement acceptables, sous la forme de granules enrobés, et
   (ii) un mélange d'excipients comprenant au moins un agent désintégrant, un agent diluant soluble, un lubrifiant.

2. Comprimés orodispersibles selon la revendication 1, qui sont aptes à se désintégrer en moins de 40 secondes.

3. Comprimés orodispersibles selon la revendication 1, dans lesquels le mélange d'excipients comprend en outre un agent gonflant, un agent antistatique, un agent perméabilisant, des édulcorants, des agents aromatisants ou des colorants.

4. Comprimés orodispersibles selon la revendication 1, dans lesquels le rapport massique du mélange d'excipients aux granules enrobés est 0,4 à 9.

5. Comprimés orodispersibles selon la revendication 4, dans lesquels le rapport massique du mélange d'excipients aux granules enrobés est 1,5 à 5.

6. Comprimés orodispersibles selon la revendication 5, dans lesquels le rapport massique du mélange d'excipients aux granules enrobés est 2 à 3.

7. Comprimés orodispersibles selon la revendication 1, dans lesquels l'agent désintégrant est choisi dans le groupe consistant en croscarmellose, crospovidone et leurs mélanges.

8. Comprimés orodispersibles selon la revendication 1, dans lesquels l'agent diluent soluble a des propriétés liantes et consiste en un polyol ayant moins de 13 atomes de carbones et qui se présente soit sous la forme d'un produit directement compressible qui a une taille moyenne de particules de 100 à 500 microns, ou sous la forme d'une poudre avec une taille moyenne de particule inférieure à 100 microns, ce polyol étant de préférence choisi dans le groupe comprenant le mannitol, le xylitol, le sorbitol et le maltitol, étant entendu que le sorbitol ne peut pas être utilisé seul et que, dans le cas où il y a seulement un agent diluant soluble avec des propriétés liantes, il est utilisé sous la forme d'un produit directement compressible, alors que dans le cas où, il y a au moins deux agent diluants solubles avec des propriétés liantes, l'un est présent sous la forme directement compressible et l'autre est présent sous la forme de poudre, les polyols pouvant être identiques, le rapport du polyol directement compressible au polyol poudre étant 99/1 à 80/20 de préférence 80/20 à 20/80.

9. Comprimés orodispersibles selon la revendication 1 dans lesquels la proportion d'agent désintégrant est de 3 à 15% en poids, et la proportion d'agent diluent soluble est de 30 à 90% en poids, les pourcentages étant calculés sur la base du poids en comprimé.

10. Comprimés orodispersibles selon la revendication 9 dans lesquels la proportion d'agents désintégrant est de 5 à 15% en poids et la proportion d'agent diluant soluble est de 40 à 60% en poids, les pourcentages étant calculés sur la base du poids total du comprimé.

11. Comprimés orodispersibles selon la revendication 1, dans lesquels le lubrifiant est choisi dans le groupe consistant en stéarate de magnésium, acide stéarique, stéaryl fumarate de sodium, polyoxyethylèneglycol micronisé, leukine, benzoate de sodium et leurs mélanges.

12. Comprimés orodispersibles selon la revendication 3, dans lesquels l'agent édulcorant est choisi dans le groupe consistant en aspartame, acesulfame de potassium, saccharinate de sodium, neohesperidin dihydrochalcone, sucralose, glycyrrhizinate de monoammonium et leurs mélanges.

13. Comprimés orodispersibles selon la revendication 11, dans lesquels le lubrifiant est sous la forme de poudre et est, au moins en partie, disposé sur la surface des comprimés.

14. Granules de fexofenadine ou d'un de ses sels pharmaceutiquement acceptables dans lesquels les granules sont

enrobés et contiennent :

- des microcristaux de fexofenadine ou d'un de ses sels pharmaceutiquement acceptables,
- au moins un liant choisi dans le groupe consistant en polymères cellulosiques, tels que l'éthylcellulose, l'hydroxypropylcellulose et l'hydroxypropylméthylcellulose, des polymères acryliques tels que le copolymère acylate ammoniométhacrylate insoluble, le copolymère polyacrylate ou polyméthacrylique, povidones, copovidones, polyvinyalcools, acid alginic, l'alginate de sodium, amidon, amidon prégeatinisé, le sucrose et ses dérivés, la gomme guar, le polyéthylène glycol et leurs mélanges.

15. Granules selon la revendication 14 qui contient en outre un agent diluant choisi dans le groupe consistant en cellulose microcristalline, sucrose, phosphate dicalcique, amidons, lactose, polyols ayant moins de 13 atomes de carbone tels que le mannitol, le xylitol, le sorbitol, le maltitol, des aminoacides pharmaceutiquement acceptables tels que la glycine, et leurs mélanges, un agent antistatique choisi dans le groupe consistant en talc micronisé ou non micronisé, fumée de silice, silice précipitée et colloïdale, un agent édulcorant ou un agent colorant.

16. Granules selon la revendication 14, qui comprend en outre un agent désintegrant choisi dans le groupe consistant en croscarmellose, crospovidone et leurs mélanges ou un agent tensioactif qui peut être anionique, non ionique, cationique ou amphotère.

17. Granules selon la revendication 15, comprenant :

- de 10 % à 95% de fexofénadine, ou un de ses sels pharmaceutiquement acceptables,
- au plus 20% en poids du liant, par rapport au poids de féxofenadine ou d'un de ses sels pharmaceutiquement acceptables,
- au plus 5% de l'agent antistatique, par rapport au poids desdits granules.

18. Granules selon la revendication 17, comprenant :

- de 50 à 70% de fexofenadine, ou d'un de ses sels pharmaceutiquement acceptables,
- au plus 10% en poids du liant, par rapport au poids de fexofenadine ou d'un de ses sels pharmaceutiquement acceptables,
- au plus 2% en poids de l'agent antistatique, par rapport au poids desdits granules.

19. Granules selon la revendication 17, comprenant en outre un agent diluant jusqu'à l'équilibre à 100%.

20. Granules selon la revendication 18, comprenant en outre un agent diluant jusqu'à l'équilibre à 100%.

21. Granules selon la revendication 14, qui sont enrobés avec une composition d'enrobage contenant au moins un polymère d'enrobage consistant en polymères cellulosiques tels que éthylcellulose, hydroxypropylcellulose et hydroxypropylméthylcellulose, polymères acryliques tels que le copolymère acrylate ammoniométhacrylate insoluble, copolymères polyacrylates ou méthacryliques, et leurs mélanges.

22. Granules selon la revendication 21, dans lesquels la composition d'enrobage contient en outre des agents perméabilisants, des plastifiants, des agents solubles, des agents désintégrants ou tensio-actifs.

23. Granules selon la revendication 22 comprenant :

- de 10% à 95% de granules de fexofenadine, ou d'un de ses sels pharmaceutiquement acceptables,
- de 5 à 90% d'un polymère d'enrobage, les pourcentages étant exprimés en poids par rapport au poids des granules de fexofenadine, ou d'un de ses sels pharmaceutiquement acceptables,
- de 0 à 10% d'un agent perméabilisant, les pourcentages étant exprimé en poids par rapport au poids du polymère d'enrobage.

24. Granules selon la revendication 23 comprenant :

- de 40 à 75% de granules de fexofenadine, ou d'un de ses sels pharmaceutiquement acceptables,
- de 10 à 70% d'un polymère d'enrobage, les pourcentages étant exprimés en poids par rapport au poids des granules de fexofenadine, ou d'un de ses sels pharmaceutiquement acceptables,

- de 0 à 10% de silice colloïdale en tant qu'agent perméabilisant, les pourcentages étant exprimés en poids par rapport au poids du polymère d'enrobage.

25. Granules selon la revendication 24, comprenant 25 à 55 % d'un polymère d'enrobage.

26. Granules selon la revendication 23, comprenant du chlorhydrate de fexofenadine.

27. Granules enrobés de fexofenadine ou d'un de ses sels pharmaceutiquement acceptables, selon la revendication 14, qui sont enrobés avec une couche d'enrobage contenant de la fexofenadine dans lesquels les granules et la couche d'enrobage comprennent chacun de 70% à 95% en poids de fexofenadine ou d'un de ses sels pharmaceutiquement acceptables, l'équilibre à 100% étant formé par au moins un liant.

28. Granules enrobés de fexofenadine, ou d'un de ses sels pharmaceutiquement acceptables, selon la revendication 27, qui sont enrobés avec une couche d'enrobage contenant de la fexofenadine dans lesquels les granules et la couche d'enrobage comprennent chacun 80% à 95% en poids de fexofenadine ou d'un de ses sels pharmaceutiquement acceptables, l'équilibre à 100% étant formé par au moins un liant.

29. Procédé de préparation de granules selon la revendication 14 comprenant les étapes successives consistant à :

- mélanger à sec les microcristaux de fexofenadine ou l'un de ses sels pharmaceutiquement acceptables,
- granuler le mélange obtenu à l'étape ci-dessus par pulvérisation d'une solution ou suspension d'au moins un liant,
- enrober les granules ainsi obtenus avec une suspension d'une composition d'enrobage,
- sécher les granules enrobés ainsi obtenus.

30. Procédé de préparation de granules selon la revendication 15, comprenant les étapes successives consistant à :

- mélanger à sec les microcristaux de fexofenadine ou d'un de ses sels pharmaceutiquement acceptables avec un agent antistatique ou un agent diluent,
- granuler le mélange obtenu à l'étape ci-dessus par pulvérisation d'une solution ou suspension d'au moins un liant,
- enrober les granules ainsi obtenus avec une suspension d'une composition d'enrobage,
- sécher les granules enrobés ainsi obtenus.

31. Procédé de préparation de granules selon la revendication 27, comprenant les étapes successives consistant à :

- sécher à sec les microcristaux de fexofenadine ou d'un de ses sels pharmaceutiquement acceptables ;
- granuler le mélange obtenu dans l'étape ci-dessus par pulvérisation d'une solution ou suspension d'au moins un liant,
- appliquer une couche sur les granules ainsi obtenus par pulvérisation sur celles-ci d'une suspension ou d'une solution comprenant de la fexofenadine ou un de ses sels pharmaceutiquement acceptables avec au moins un liant,
- enrober les granules ainsi obtenus avec une suspension d'une composition d'enrobage,
- sécher les granules enrobés ainsi obtenus.

32. Procédé selon la revendication 31, comprenant les étapes successives consistant à :

- sécher à sec les microcristaux de fexofenadine ou d'un de ses sels pharmaceutiquement acceptables avec un agent antistatique ou un agent diluant ;
- granuler le mélange obtenu à l'étape ci-dessus par pulvérisation d'une solution ou d'une suspension d'au moins un liant,
- appliquer une couche sur les granules ainsi obtenues par pulvérisation d'une solution ou suspension d'au moins un liant,
- enrober les granules ainsi obtenus avec une suspension d'une composition d'enrobage,
- sécher les granules enrobés ainsi obtenus.

33. Procédé de préparation de comprimés selon la revendication 1, comprenant les étapes successives de :

- préparation de granules enrobés de fexofenadine, ou d'un de ses sels pharmaceutiquement acceptables,
- séchage à sec des granules enrobés et d'un mélange d'excipients comprenant au moins un agent désintégrant et un agent diluant soluble,
- compression du mélange de granules enrobés et d'excipients en un comprimé.

34. Procédé de préparation de comprimés selon la revendication 33 , dans lequel le mélange d'excipients comprend en outre un lubrifiant, un agent perméabilisant, un agent gonflant, des édulcorants, un agent antistatique, des agents aromatisants et colorants.

35. Utilisation d'une composition contenant:

(i) de la fexofenadine, ou au moins un de ses sels pharmaceutiquement acceptables, sous la forme de granules enrobés, et
(ii) un mélange d'excipients comprenant au moins agent désintégrant, un agent diluant soluble, un lubrifiant,

pour la fabrication d'un comprimé orodispersible selon la revendication 1, destiné à être administré par voie orale à des patients souffrants de symptômes associés à une rhinite allergique saisonnière.