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(54) **CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITIONS**

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(57) **ABSTRACT**

The invention relates to an oral pharmaceutical composition comprising an active agent, a macroscopically homogeneous structure and a gastro-resistant coating. The macroscopically homogeneous structure comprises at least one hydrophilic compound and at least one lipophilic compound and/or at least one amphiphilic compound. The macroscopically homogeneous structure controls the release of the active ingredient, and the gastro-resistant film prevents release of the active agent in the stomach.

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CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 13/617,138 filed on Sep. 14, 2012, now U.S. Pat. No. 8,784,888; which is a continuation of application Ser. No. 13/462,409 filed on May 2, 2012, now U.S. Pat. No. 8,293,273; which is a continuation of Ser. No. 13/249,839 filed on Sep. 30, 2011, now abandoned; which is a continuation of application Ser. No. 12/210,969 filed on Sep. 15, 2008, which reissued as U.S. Pat. No. RE43,799 from U.S. Pat. No. 8,029,823; which is a continuation-in-part of application Ser. No. 10/009,532 filed on Dec. 12, 2001, now U.S. Pat. No. 7,431,943; which is the 35 U.S.C. 371 national stage of International application PCT/EP00/05356 filed on Jun. 9, 2000; which claimed priority to Italian applications MI2000A000422 and MI99A001317 filed Mar. 3, 2000 and Jun. 14, 1999, respectively. The entire contents of each of the above-identified applications are hereby incorporated by reference.

The present invention relates to controlled release and taste-masking compositions containing one or more active principles incorporated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally incorporated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract, and it also allows the oral administration of active principles having unfavourable taste characteristics or irritating action on the mucosae of the administration site, particularly in the buccal area.

The compositions of the invention can contain active principles belonging to the therapeutical classes of analgesics, antiinflammatories, cardioactives, tranquillizers, antihypertensives, disinfectants and topical antimicrobials, antiparkinson drugs, antihistamines and are suitable to the oral administration or for acting topically at some areas of the gastrointestinal tract.

TECHNOLOGICAL BACKGROUND

The preparation of a sustained, controlled, delayed or anyhow modified release form can be carried out according to different known techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Hydrophilic matrices have a linear behaviour until a certain fraction of active ingredient has been released; then they significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "site-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated.

The same notion of canalization of an inert matrix is described in U.S. Pat. No. 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials.

EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form.

The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533, (1998) which improves the application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:

- dissolution of the active ingredient with gastro-resistant hydrophilic polymers in organic solvents;
- drying of said suspension;
- subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application.

EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid.

WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of the active ingredient.

When preparing sustained-, controlled-release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release.

Said object has been attained according to the present invention, through the combination of an amphiphilic matrix inside an inert matrix, the latter formulated with a lipophilic polymer in a superficial hydrophilic matrix. The composi-

the matrix is quickly solubilized, and by the fact the amphiphilic layer compensate the lack of affinity of the aqueous solvent with the lipophilic compounds forming the inner inert matrix.

DISCLOSURE OF THE INVENTION

The invention provides controlled release and taste masking oral pharmaceutical compositions containing an active ingredient, comprising:

a) a matrix consisting of lipophilic compounds with melting point lower than 90° C. and optionally by amphiphilic compounds in which the active ingredient is at least partially incorporated;

b) optionally an amphiphilic matrix;

c) an outer hydrophilic matrix in which the lipophilic matrix and the optional amphiphilic matrix are dispersed;

d) optionally other excipients.

A particular aspect of the invention consists of controlled release oral compositions containing one or more active ingredients comprising:

a) a matrix consisting of amphiphilic compounds and lipophilic compounds with melting point below 90° C. in which the active ingredient is at least partially incorporated;

b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed;

c) optional other excipients.

A further aspect of the invention provides taste masking oral pharmaceutical compositions containing one or more active ingredients comprising:

an inert or lipophilic matrix consisting of C6-C20-alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six;

an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;

an outer hydrophilic matrix containing the above matrices, mainly formed by saccharide, dextrin, polyalcohol or cellulose compounds or by hydrogels;

optional excipients to give stability to the pharmaceutical formulation.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be prepared by a method comprising the following steps:

a) the active ingredient is first inglobated by simple kneading or mixing in a matrix or coating consisting of compounds having amphiphilic properties, which will be further specified below. The active principle(s) can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.

b) The matrix obtained in a) is incorporated in a low melting lipophilic excipient or mixture of excipients, while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion. After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.

c) The inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients. The mixture is then subjected to compression or tabletting. This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to

caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

The amphiphilic compounds which can be used according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol®).

The lipophilic matrix consists of substances selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerides, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having a melting point within the range of 40 to 90° C., preferably from 60 to 70° C.

If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

According to an embodiment of the invention, an amphiphilic matrix with high content in active ingredient, typically from 5 to 95% w/w, is first prepared by dispersing the active ingredient or the mixture of active ingredients in a mixture of amphiphilic compounds, such as lecithin, other type II polar lipids, surfactants, or in diethylene glycol monoethyl ether; the resulting amphiphilic matrix is then mixed or kneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, such as saturated or unsaturated fatty acids, such as palmitic, stearic, myristic, lauric, laurylic, or oleic acids or mixtures thereof with other fatty acids with shorter chain, or salts or alcohols or derivatives of the cited fatty acids, such as mono-, di-, or triglycerides or esters with polyethylene glycols, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios so that the melting or softening points of the lipophilic compounds mixtures is within the range of 40 to 90° C., preferably from 60 to 70° C.

Alternatively, the order of formation of the inert and amphiphilic matrices can be reversed, incorporating the inert matrix inside the amphiphilic compounds.

The resulting inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which when passing from the dry state to the hydrated one, undergo the so-called “molecular relaxation”, namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

Examples of hydrogels which can be used according to the invention are compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

In case of taste-masking formulations, the use of polyalcohols such as xylitol, maltitol and mannitol as hydrophilic compounds can also be advantageous.

The lipophilic matrix granules containing the active ingredient are mixed with the hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:50

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