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

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(57) **ABSTRACT**

Controlled release and taste masking compositions containing one or more active principles inglobated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally inglobated 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.

Exhibit 1011

### CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION

[0001] The present invention relates to controlled release and taste masking compositions containing budesonide as active ingredient 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 mechanism 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 or gastric area.

[0002] The compositions of the invention are suitable to the oral administration or the efficaciously deliver the active ingredient acting topically at some areas of the gastrointestinal tract.

#### TECHNOLOGICAL BACKGROUND

[0003] The preparation of a sustained, controlled, delayed, extended or anyhow modified release form can be carried out according to different techniques:

[0004] 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.

[0005] 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.

[0006] 3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

[0007] All the procedures listed above suffer, however, from drawbacks and imperfections.

[0008] Inert matrices, for example, generally entail non-linear, but exponential, release of the active ingredient.

[0009] Hydrophilic matrices: have a linear behaviour until a certain fraction of active ingredient has been released, then significantly deviate from linear release.

[0010] Bioerodible matrices are ideal to carry out the so-called "sire-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.

[0011] 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

[0012] 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 penetration 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.

[0013] 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 compositions of the invention are characterized by the absence of a first phase in which the medicament superficially present on 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

[0014] The invention provides controlled release and taste masking oral pharmaceutical compositions containing as active ingredient budesonide comprising:

[0015] 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;

- [0016] b) an amphiphilic matrix;
- [0017] c) an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed;
- [0018] d) optionally other excipients.
- [0019] A particular aspect of the invention consists of controlled release oral compositions containing as active ingredient budesonide comprising:
- [0020] 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;
- [0021] b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed, preferably by mixing;
- [0022] c) optionally other excipients.
- [0023] A further aspect of the invention provides taste masking oral pharmaceutical compositions budesonide containing comprising:
- [0024] 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;
- [0025] an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;
- [0026] an outer hydrophilic matrix containing the above matrices, mainly formed by saccharide, dextrin, polyalcohol or cellulose compounds or by hydrogels or their mixtures;
- [0027] optional excipients to give stability to the pharmaceutical formulation.

#### DETAILED DISCLOSURE OF THE INVENTION

- [0028] The compositions of the invention can be prepared by a method comprising the following steps:
- [0029] a) the active ingredient, represented by budesonide, 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 ingredient can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.
- [0030] b) the matrix obtained as specified under a) is incorporated in a low melting lipophilic excipient or mixture of excipients, if necessary while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion forming an inert matrix which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.
- [0031] c) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swallowable excipients. The mixture is then subjected to compression or tableting. 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 penetration of the

aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" 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<sup>®</sup>). 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 triglycerids, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having 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. An amphiphilic matrix with high content in active ingredient, typically from 5 to 95% w/w, in particular from 20 to 70%, is first prepared by dispersing the active ingredient 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 triglycerids 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, dextrans, 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 lipo-

philic 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 (lipophilic matrix: hydrophilic matrix). Part of the active ingredient can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitables. The compression of the mixture of lipophilic and/or amphiphilic matrix, hydrogel-forming compound and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix. A similar result can also be obtained by coating the lipophilic matrix granules with a hydrophilic polymer coating. The tablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of, for example, acrylic and methacrylic acids polymers (Eudragit (R)) or copolymer or cellulose derivatives, such as cellulose acetophthalate. The composition of the invention can further contain conventional excipients, for example bioadhesive excipients such as chitosans, polyacrylamides, natural or synthetic gums, acrylic acid polymers.

[0032] The compositions of the invention are preferably in the form of tablets, capsules or minitables. In terms of dissolution characteristics, contact with water or aqueous fluids causes the immediate penetration of water inside the more superficial layer of the matrix which, thanks to the presence of the aqueous solvent, swells due to the distension of the polymeric chains of the hydrogels, giving rise to a high viscosity hydrated front which prevents the further penetration of the solvent itself linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness, until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of inert matrix granules, however induces the diffusion mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient. The presence of the amphiphilic matrix inside the lipophilic matrix inert allows to prevent any unevenness of the release profile of the active ingredient. The surfactants present in the amphiphilic portion promote wettability of the porous canaliculuses which cross the inert matrix preventing or reducing resistance to penetration of the solvent inside the inert matrix. To obtain taste masking tablets, the components of the hydrophilic matrix are carefully selected to minimize the active substance release time through penetration accelerated by the canalization induced by the hydrophilic compound.

#### EXPERIMENTAL PART

[0033] To test the effective ability of the formulations of the invention to modify the release rate and extent of the active ingredient from the dosage form suitable for the drug administration, before any pharmacokinetic study on patients or volunteers, the dissolution test is taken as monitoring and discriminating tool.

#### Dissolution Test Method

[0034] Tablets according to the present invention undergo to dissolution test to verify the formulation capacity in modulating and controlling the rate by which the active ingredient is leaked by the device or dosage form in the environmental medium, generally a buffered solution simulating gastric or intestinal juices.

[0035] The dissolution test is performed by introducing individual tablets in a glass vessel containing from 500 to 1000 ml of a buffered solution set to different pH conditions (pH 1, 6.4 and 7.2 are the pH condition generally used in this test applications), so that the whole digestive tract pH conditions, from stomach to large intestine, should be reproduced. To simulate the human body conditions, the test is carried out at a temperature of  $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ . and at predetermined time periods samples of the dissolution medium are withdrawn to detect the percentage of active ingredient dissolved over time.

[0036] The tablets according to the present invention, when designed to be used to treat inflammatory bowel disease, in principle have to show a good resistance, thanks to the polymeric film resistant to the low pH conditions (intended as <5 to simulate the gastric environment) applied to cover the tablet surface, resistance which last at least for two hours; to target the large intestinal sectors, also the pH condition of 6.4 shown unsuitability to determine a drug leakage from the administration device for a short exposition time and only mediums at pH 7.2 have been able to determine an active ingredient dissolution at a progressive and quite constant rate during a timeframe from 6 to 12 hours; the dissolution percentage obtained with this tablet formulation were below 15% at first hour sampling, below 25% at second hour sampling, then values were in the range 25% to 55% at fourth hour and a dissolution greater than 80% was achieved at 8<sup>th</sup> hour sampling.

#### EXAMPLE 1

[0037] 2.7 kg of budesonide, 3.0 kg of lecithin (amphiphilic matrix forming material) and 3.0 kg of stearic acid (lipophilic matrix forming material) are mixing after sieving till an homogeneous mixture is obtained; then add 39.0 kg of inert, functional excipients and 9.0 kg of low viscosity hydroxypropylcellulose (binder) and mix for 10 minutes before adding purified water and kneading to a suitable consistence. Then pass the granulate through a rotating granulator equipped with the suitable screen and transfer the granulate to the fluid bed drier to lower the residual moisture content under 3%.

[0038] After a new sieving on the dry, the granulate is added of 9.0 kg of hydroxypropylcellulose (hydrophilic matrix forming material) and the suitable amount of functional excipients (in particular, microcrystalline cellulose, lactose and silicon dioxide)

[0039] and, after 15 minutes of mixing, magnesium stearate in a suitable quantity to act as lubricant is added.

[0040] After a final blending, tablets of around 300 mg of unitary weight are generated.

[0041] The core are then subjected to be coated with a suspension obtained introducing into a stainless steel con-

tainer 5.8 kg of Eudragit™ (methacrylate copolymers), 0.6 kg of triethylcitrate and 3.0 kg of dyes and talc, using alcohol as solvent.

[0042] The mean dissolution percentage (as average of six or more tablets) obtained with this tablet formulation were around 10-20% at second hour sampling, in the range 25% to 65% at fourth hour and a dissolution greater than 80% was achieved at 8<sup>th</sup> hour sampling.

## EXAMPLE 2

[0043]

Component	mg/tablet
<u>Tablet</u>	
Budesonide	9.0
Stearic Acid	10.0
Lecithin	10.0
Microcrystalline cellulose	156.0
Hydroxypropylcellulose	60.0
Lactose monohydrate	50.0
Silicon dioxide	2.0
Magnesium stearate	3.0
<u>Coating materials</u>	
Eudragit L100	14.0
Eudragit S100	12.0
Talc	7.9
Titanium dioxide	4.5
Triethylcitrate	1.6
Alcohol	q.s.

[0044] According to the present invention, coated tablets individually weighing about 220 mg are obtained.

[0045] The above described dissolution test is performed on the tablets of Example 2.

[0046] The results are the following (indicated as average value):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	15%
after 4 hours at pH 7.2	37%
after 8 hours at pH 7.2	91%

## EXAMPLE 3

[0047] Budesonide (3.0 kg) is mixed with soybean Lecithin (5.0 kg) till an homogeneous mixture is obtained. Then carnauba wax (2.0 kg) and stearic acid (2.0 kg) sieved through a fine screen are added. After mixing, the powders are added with other functional excipients and kneaded with a binder solution obtained by dissolving medium viscosity polyvinylpyrrolidone in water. After drying in a fluid bed and milling throughout a suitable screen, hydroxypropylmethylcellulose (35.0 kg) and other excipients, including magnesium stearate as lubricant, in a suitable quantity are added and the mixture is blended till an homogeneous powder dispersion is obtained.

[0048] The powder mixture is subjected to compression in a rotating tableting machine and the tablets so obtained are

coated in a pan coat with a gastroresistant composition containing Eudragit™, plasticizers, dyes and pigments.

[0049] According to the present example, coated tablets individually weighing around 105 mg are obtained.

[0050] The results of the above described dissolution test are the following (indicated as average value of at least six tablets):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	9%
after 4 hours at pH 7.2	28%
after 8 hours at pH 7.2	86%

## EXAMPLE 4

[0051] 50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 60° C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm. A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of Polycarbophil™ are added. The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g of magnesium stearate. After further 5 minute mixing, the mix is tableted to unitary weight of 250 mg/tablet.

[0052] Tablets are then subjected to coating using a suspension containing polyacrylate and poly methacrylate copolymers in addition to other dyes, plasticizers and colouring agents in solvent (ethyl alcohol).

[0053] The results of the dissolution test performed on these coated tablets are the following (indicated as average value of at least six tablets):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	11%
after 4 hours at pH 7.2	32%
after 8 hours at pH 7.2	76%

1. Controlled release and taste-masking oral pharmaceutical compositions containing budesonide as active ingredient comprising:

- a matrix consisting of lipophilic compounds with melting point lower than 90 C in which the active ingredient is at least partially inglobated;
- an amphiphilic matrix;
- an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed;
- optionally other excipients.



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