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

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(56) References Cited

U.S. PATENT DOCUMENTS

5,320,848 A 6/1994 Geyer et al.
 5,342,625 A * 8/1994 Hauer et al. 424/455
 5,534,501 A 7/1996 Samain et al.
 5,597,844 A 1/1997 Chauhan et al.
 5,643,602 A * 7/1997 Ulmuis 424/462
 5,681,584 A 10/1997 Savastano et al.
 5,811,388 A 9/1998 Friend et al.
 5,840,332 A 11/1998 Lerner et al.
 5,908,833 A 6/1999 Brattsand et al.
 5,965,167 A 10/1999 Sanghvi et al.
 6,140,308 A 10/2000 Brattsand et al.
 6,190,692 B1 2/2001 Buseti et al.

6,258,377 B1 7/2001 New et al.
 6,368,635 B1 4/2002 Akiyama et al.
 6,562,363 B1 5/2003 Mantelle et al.
 7,410,651 B2 8/2008 Villa et al.
 7,410,652 B2 8/2008 Villa et al.
 7,431,943 B1 10/2008 Villa et al.
 8,029,823 B2 10/2011 Villa et al.
 2012/0021052 A1 1/2012 Villa et al.
 2012/0021053 A1 1/2012 Villa et al.

FOREIGN PATENT DOCUMENTS

CA 2 119 253 11/1998
 DE 41 31 562 3/1993
 DE 41 31 562 A1 3/1993
 EP 0 482 576 4/1992
 EP 0 514 008 11/1992
 EP 0 514 008 A1 11/1992
 GB 935639 9/1963
 JP 63048226 2/1988
 JP 4159217 6/1992
 JP 5132416 5/1993
 JP 6510772 12/1994
 JP 6511478 12/1994
 JP 8503482 4/1996
 JP 2000510488 8/2000
 JP 2000515130 11/2000
 WO WO 96/13273 5/1996
 WO WO 98/00169 1/1998
 WO WO 99/11245 3/1999
 WO WO 99/17752 4/1999

OTHER PUBLICATIONS

Moro et al., "Drug Delivery Systems: Diffusion Controlled Systems," II Prodotto Chimico & Aerosol Selezione (The Chemical & Aerosol Selection), Apr. 1985, pp. 16-24, Partial relevant English translation of pp. 20 and 22 included.
 Steward, "Review of Pharmaceutical Controlled Release Methods and Devices," 1995, pp. 1-9.
 Physical Pharmacy, Chapter 19: Drug Product Design, Oct. 1993, pp. 515-519.
 JP Office Action dated May 6, 2010 from corresponding JP2001-502812, English translation included.
 "Budesonide"—Wikipedia, the free encyclopedia, (<http://en.wikipedia.org/wiki/Budesonide>); pp. 1-3.

(Continued)

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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.

11 Claims, No Drawings

OTHER PUBLICATIONS

Jantzen, G.M. et al. "Sustained— and Controlled-Release Drug Delivery Systems," *Modern Pharmaceutics*, 3rd Edition, Revised and Expanded, pp. 575-609, © 1996 by Marcel Dekker, Inc., 37 pages.

Brunner, M. et al., "Gastrointestinal Transit, Release and Plasma Pharmacokinetics of a New Oral Budesonide Formulation," *British Journal of Clinical Pharmacology*, DOI:10.1111/j.1365-2125.2005.02517.x, pp. 1-8, copyright 2005 Blackwell Publishing Ltd., 8 pages.

Brunner, M. et al., "Gastrointestinal Transit and 5-ASA Release From a New Mesalazine Extended-Release Formulation," *Alimentary Pharmacology and Therapeutics*, vol. 17, pp. 395-402, copyright 2003 Blackwell Publishing Ltd., 8 pages.

Angelucci et al., "Budesonide for Inflammatory Bowel Disease Treatment," *Current Medicinal Chemistry*, 2008, vol. 15, No. 14, pp. 2-9.

D'Haens, G.R. et al., "Budesonide MMX™ Is Active and Safe In Patients With Active Left-Sided Ulcerative Colitis," *Br J Clin Pharmacol.*, 2005, vol. 61, 3 pages.

Maejima, T., "Application of Tumbling Melt Granulation Method to Prepare Controlled-Release Beads by Coating with Mixture of Functional Non-Meltable and Meltable Materials," *Chem. Pharm. Bull.*, 1998, vol. 46, No. 3, pp. 531-533, © 1998 Pharmaceutical Society of Japan.

Sandborn, W.J. et al., "Budesonide MXX® 9 mg For The Induction of Remission of Mild-to-Moderate Ulcerative Colitis (UC): Data From a Multicenter, Randomized, Double-Blind Placebo-Controlled Study in North America and India," *Presentation at DDW 2011*, Poster, 1 page.

D'Haens, G.R., et al., "Clinical Trial: Preliminary Efficacy and Safety Study of a New Budesonide-MMX® 9 mg Extended-Release Tablets in Patients With Active Left-Sided Ulcerative Colitis," *Journal of Crohn's and Colitis*, 2010, vol. 4, pp. 153-160, © copyright 2009 European Crohn's and Colitis Organisation.

Flanders, P. et al., *The Control of Drug Release From Conventional Melt Granulation Matrices*, Drug Development and Industrial Pharmacy, 1987, vol. 13, No. 6, pp. 1001-1022, © 1987 Marcel Dekker, Inc.

Ferraboschi, P. et al., "Estimation and Characterisation of Budesonide Tablets Impurities," *Journal of Pharmaceutical and Biomedical Analysis*, 2008, vol. 47, pp. 636-640, © 2008 Elsevier B.V.

Fiorino, G. et al., "New Drug Delivery Systems in Inflammatory Bowel Disease: MMX™ and Tailored Delivery to the Gut," *Current Medicinal Chemistry*, 2010, vol. 17, pp. 1851-1857, © 2010 Bentham Science Publishers Ltd.

Koutroubakis, I., "Recent Advances in the Management of Distal Ulcerative Colitis," *World Journal of Gastrointestinal Pharmacology and Therapeutics*, 2010, vol. 1, No. 2, pp. 43-50, © 2010 Baishideng. JP Office Action dated May 6, 2010 from corresponding JP2001-502812—English translation included.

Steward, P., "Review of Pharmaceutical Controlled Release Methods and Devices", 1995, pp. 1-9.

Moro, et al., "Drug Delivery Systems: Diffusion Controlled Systems", *Il Prodotto Chimico & Aerosol Selezione (The Chemical & Aerosol Selection)*, Apr. 1985, pp. 16-24, Partial relevant English translation of pp. 20 and 22 included.

* cited by examiner

CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in *italics* indicates the additions made by reissue.

This application is a continuation-in-part application of U.S. application Ser. No. 10/009,532, filed Dec. 12, 2001, which is a national stage of International Application No. PCT/EP00/05356 on Jun. 9, 2000, now U.S. Pat. No. 7,431,943, the entire content of which International Application is hereby incorporated by reference and priority to which is hereby claimed.

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.

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

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

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

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

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.

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 compenetrating 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 an 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; —dyeing 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 compensates 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 as active ingredient budesonide comprising:

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

- c) an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed;
d) optionally other excipients.

A particular aspect of the invention consists of controlled release oral compositions containing as active ingredient budesonide 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, preferably by mixing;
c) optionally other excipients.

A further aspect of the invention provides taste masking oral pharmaceutical compositions budesonide containing 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 or their mixtures;

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, 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.

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.

c) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellaable 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®). 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 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 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, 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 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 (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 minitabets. 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 are subjected to known coating processes with a gastro-resistant film, consisting of, for example, acrylic and methacrylic acids polymers (Eudragit®) 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.

The compositions of the invention are preferably in the form of tablets, capsules or minitabets. In terms of dissolu-

tion 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

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.

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.

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° C. \pm 2° C. and at predetermined time periods samples of the dissolution medium are withdrawn to detect the percentage of active ingredient dissolved over time.

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 hour sampling.

Example 1

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%.

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

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

The core are then subjected to be coated with a suspension obtained introducing into a stainless steel container 5.8 kg of Eudragit™ (methacrylate copolymers), 0.6 kg of triethylcitrate and 3.0 kg of dyes and talc, using alcohol as solvent.

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 hour sampling.

Example 2

Component mg/tablet	
Tablet	
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
Coating materials	
Eudragit L100	14.0
Eudragit S100	12.0
Talc	7.9
Titanium dioxide	4.5
Triethylcitrate	1.6
Alcohol	q.s.

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

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

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

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.

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.

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

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	(<5%) resistant
after 1 hour at pH 6.4	(<5%) resistant
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

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[deg.] 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 tabletted to unitary weight of 250 mg/tablet.

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

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

EXAMPLE A

500 g of 5-aminosalicylic-acid and 20 of octylonium bromide are mixed with 10 g of soy lecithin dissolved in 50 g of a water:ethyl alcohol 1:3 mixture at about 50° C. After homogenization and drying, the granules of the resulting matrix are treated in a kneader with 20 g of carnauba wax and 50 g of stearic acid, heating until homogeneous dispersion, then cold-extruded into small granules. The inert matrix granules are loaded into a mixer in which 30 g of carbopol 971 P and 65 g of hydroxypropyl methylcellulose "are sequentially added." After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 760 mg/tablet. The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 30%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

EXAMPLE B

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.

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 tabletted to unitary weight of 250 mg/tablet.

EXAMPLE C

850 g of metformin are dispersed in a granulator/kneader with 35 g of diethylene glycol monoethyl ether previously melted with 100 g of stearic acid and 55 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 1040 g of formulation are added with 110 g of hydroxypropyl methylcellulose and 20 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 1170 mg/tablet equivalent to 850 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 35%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

EXAMPLE D

120 g of octylonium bromide are dispersed in a granulator/kneader with 30 g of stearic acid and 15 g of beeswax in which 10 g of diethylene glycol monoethylene had previously been melted.

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The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 10 g of formulation are added with 5 g of hydroxypropyl methylcellulose and 5 g of polycarbophil, 2 g of magnesium stearate and 3 g of microcrystalline cellulose.

The final mixture is tableted to unitary weight of 200 mg/tablet equivalent to 120 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 25%; after 180 minutes no more than 50%; after 5 hours no more than 70%.

EXAMPLE E

12 g of diethylene glycol monoethyl ether are loaded on 6 g of microcrystalline cellulose and 6 grams of calcium carbonate, then 100 g of Gabapentin are added and the mixture is homogenized. After that, 800 g of Gabapentin are added which are dispersed in a granulator/kneader with 4.5 g of white wax and 5 g of stearic acid. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 916.5 g of formulation are added with 39.5 g of hydroxypropyl methylcellulose, 10 g of alginic acid, 11 g of magnesium stearate and 6 g of syloid. The final mixture is tableted to unitary weight of 1000 mg/tablet equivalent to 900 mg of active ingredient.

EXAMPLE F

50 g (25 g) of carbidopa and 200 g (100 g) of levodopa are dispersed in a granulator/kneader with 60 g (30 g) of stearic acid and 30 g (15 g) of yellow wax, in which 10 (5) g of diethylene glycol monoethyl ether had previously been melted.

The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 340 g (170 g) of formulation are added with 20 g (10 g) of hydroxypropyl methylcellulose, 10 g (5 g) of xantangum, 16 g (8 g) of microcrystalline cellulose, 4 g (2 g) of magnesium stearate.

The final mixture is tableted to unitary weight of 400 (200) mg/tablet equivalent to 50 (25) mg of carbidopa and 200 (-100) mg di levodopa.

EXAMPLE G

4 g of Nimesulide are solubilised in 50 g of diethylene glycol monoethyl ether, then 100 g of microcrystalline cellulose are added to obtain a homogeneous mixture.

The resulting mixture is added in a granulator/kneader with 196 g of Nimesulide, 50 g of stearic acid and 25 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert and amphiphilic matrix system.

425 g of the resulting granulate are added with 60 g of hydroxypropyl methylcellulose, 5 g of polycarbophil and 10 g of magnesium stearate.

The final mixture is tableted to unitary weight of 500 mg/tablet equivalent to 200 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 1 hour no more than 25%, after 2 hours no more than 40%, after 4 hours no more than 60%, after 8 hours no more than 90%.

EXAMPLE H

500 g of propionyl carnitine are dispersed in a granulator/kneader with 90 g of stearic acid and 40 g of carnauba wax,

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in which 20 g of diethylene glycol monoethyl ether had previously been melted. The system is heated to carry out the granulation of the active ingredient in the inert/amphiphilic matrix. The resulting 650 g of formulation are added with 60 g of hydroxypropyl methylcellulose and 10 g of magnesium stearate.

The final mixture is tableted to unitary weight of 720 mg/tablet equivalent to 500 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 40%, after 180 minutes no more than 60%, after 4 hours no more than 80%, after 8 hours no more than 90%.

EXAMPLE I

One kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with 200 g of cetyl alcohol and 25 g of glycerol palmitostearate the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30° C. The resulting inert matrix is added, keeping stirring and kneading during cooling, with 50 g of soy lecithin and 50 g of ethylene glycol monoethyl ether. The granulate is extruded through a metallic screen of suitable size and mixed with 50 g of hydroxypropyl methylcellulose, 1320 kg of maltodextrins, 2 kg of lactose-cellulose mixture, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tableted to unitary weight of about 500 mg, having hardness suitable for being dissolved in the mouth and a pleasant taste.

EXAMPLE J

Operating as in the preceding example, chewable tablets are prepared replacing dextrin with mannitol and the lactose-cellulose mixture with xylitol. The resulting tablets have pleasant taste and give upon chewing a sensation of freshness enhancing the flavour.

EXAMPLE K

Operating as described in example I, but with the following components:

active ingredient: ibuprofen	mg	100
lipophilic/inert matrix component: cetyl alcohol	mg	15
amphiphilic matrix component: soy lecithin	mg	8
hydrophilic matrix components: mannitol	mg	167
maltodextrins	mg	150
methylhydroxypropylcellulose	mg	30
adjuvants: aspartame	mg	15
flavour	mg	5
colloidal silica	mg	5
magnesium stearate	mg	5

500 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the bitter, irritating taste of the active ingredient.

EXAMPLE L

Operating as described in example I, but with the following components:

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active ingredient: diclofenac sodium	mg	25
lipophilic/inert matrix component: cetyl alcohol	mg	5
glycerol palmitostearate	mg	5
amphiphilic matrix component: soy lecithin	mg	7
hydrophilic matrix components: xylitol	mg	168
maltodextrins	mg	150
hydroxypropylmethylcellulose	mg	20
adjuvants: aspartame	mg	5
flavour	mg	5
colloidal silica	mg	5
magnesium stearate	mg	5

400 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE M

Operating as described in example I, but with the following components:

active ingredient: chlorhexidine	mg	2.5
lipophilic/inert matrix component: cetyl alcohol	mg	0.5
glycerol palmitostearate	mg	0.5
amphiphilic matrix component:	mg	0.3
diethylene glycol monoethyl ether hydrophilic matrix components: xylitol	mg	38
maltodextrins	mg	96
hydroxypropyl methylcellulose	mg	10
adjuvants: aspartame	mg	3
flavour	mg	5
colloidal silica	mg	2
magnesium stearate	mg	2

150 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE N

One Kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with g 125 of cetyl alcohol: the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30° C., then added with g 30 of lecithin. The resulting matrix is then extruded through a metallic screen of suitable size and mixed with 2.415 kg of lactose, 1.0 kg of maltodextrins, 50 g of hydroxypropyl methylcellulose, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to about 500 mg tablets, having hardness suitable for being dissolved in the mouth and pleasant taste.

The invention claimed is:

1. A controlled release and taste-masking oral pharmaceutical composition comprising:

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budesonide as an active ingredient incorporated into a matrix structure consisting essentially of:

- a) a lipophilic matrix consisting of lipophilic compounds with a melting point between 40° C. and 90° C. in which the active ingredient is at least partially inglobated;
 - b) an amphiphilic matrix;
 - c) an outer hydrophilic matrix consisting of hydrogels in which the lipophilic matrix and the amphiphilic matrix are dispersed; and
- a gastro-resistant coating wherein the active ingredient is dispersed both in the hydrophilic matrix and in the lipophilic/amphiphilic matrix, and the composition is in the form of tablets, capsules or minitabets.

2. The composition according to claim 1, wherein the active ingredient is mixed and at least partially inglobated in the amphiphilic matrix.

3. The composition according to claim 1, wherein the active ingredient is mixed and at least partially inglobated in the lipophilic matrix.

4. The composition according to claim 1, wherein the lipophilic matrix consists 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.

5. The composition according to claim 1, wherein the amphiphilic matrix consists amphiphilic compounds selected from the group consisting of polar lipids of type I or II, ceramides, glycol alkyl ethers, esters of fatty acids with polyethylene glycols, and diethylene glycols.

6. The composition according to claim 1, wherein the lipophilic matrix consists of a compound selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, mono-, di- or triglycerides of fatty acids, the polyethoxylated derivatives thereof, waxes, and cholesterol derivatives.

7. The composition according to claim 1, wherein the hydrophilic matrix consists of compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkylcellulose, carboxyalkylcellulose, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums, polyalcohols.

8. The composition according to claim 1, wherein the gastro-resistant coating consists of acrylic and methacrylic acid polymers or copolymer or cellulose derivatives.

9. The composition according to claim 1, further comprising bioadhesive substances.

10. The composition according to claim 1, wherein the composition is in tablet form, and said tablet form is chewable or erodible in the buccal cavity or in the first portion of the gastrointestinal tract.

11. A method for the treatment a subject suffering from Inflammatory Bowel Disease and Irritable Bowel Syndrome, comprising administering an effective amount of the pharmaceutical composition according to claim 1 to a subject in need of such a treatment.

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