PATENT
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Attorney Docket No. 3850-125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
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Roberto VILLA *et al.*	)	Group Art Unit: TBD
	)	
Application No.: TBD	)	Examiner: TBD
	)	
Filed: Herewith	)	
	)	
For: CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION	)	Confirmation No.: TBD

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

LETTER ACCOMPANYING CONTINUATION APPLICATION

The present application is a continuation of application Serial No. 13/462,409 to pursue the claims as set forth in the present application.

Claim Support

Support for these claims can be found throughout the specification and claims of parent application Serial No. 13/462,409 as filed, for example, at least as follows, with reference to the parent patents:

	Claim recitation	Support in Patent No. 8,029,823	Support in Patent No. 7,431,943
1	"A controlled release oral pharmaceutical composition"	Title of application	Title of application

Exhibit 1059

	"a tablet core"	col. 4, lines 46-50; col. 3, lines 35-36; col. 7, lines 35-36	col. 4, lines 59-63; col. 3, lines 41-42; col. 6, lines 49-50
	"budesonide in an amount effective for treatment of inflammatory bowel disease in the gastrointestinal tract"	col. 5, lines 38-39; col. 1, lines 19-21; col. 2, lines 29-32	col. 5, lines 18-20, col. 1, lines 18-24; col. 2, lines 34-37
	"a lipophilic excipient"	col. 3, line 28	col. 3, line 33
	"an amphiphilic excipient"	col. 3, line 22	col. 3, lines 27-28
	"a hydrogel forming hydrophilic excipient"	col. 3, line 34 to col. 5, line 2	col. 3, line 39 to col. 4, line 38
	"a coating on said tablet core, said coating comprising a gastro-resistant film"	col.4, lines 46-50	col.4, lines 49-53
2	"comprising 9 mg of budesonide"	col. 6, lines 20-40	---

Therefore, no new matter is added by the claims of the present application. Applicants respectfully request that the examination of this application proceed with the present claims.

Authorization to Charge Deposit Account

Please grant any extensions of time required to enter this paper and charge any additional required fees to Deposit Account No. 02-2135.

Respectfully submitted,

Dated: 14 September 2012

By /Jeffrey L. Ihnen/

Jeffrey L. Ihnen
Registration No. 28,957
Attorney for Applicants
607 14th Street, N.W., Suite 800
Washington, D.C. 20005
Phone: 202-783-6040
Fax: 202-783-6031

Controlled Release and Taste-Masking Oral Pharmaceutical Composition

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of application Serial No. 13/462,409 filed on May 2, 2012; which is a continuation of application Serial No. 13/249,839 filed on September 30, 2011; which is a continuation of application Serial No. 12/210,969 filed on September 15, 2008, now U.S. Patent No. 8,029,823; which is a continuation-in-part of application Serial No. 10/009,532 filed on December 12, 2001, now U.S. Patent No. 7,431,943; which is the 35 U.S.C. 371 national stage of International application PCT/EP00/05356 filed on June 9, 2000; which claimed priority to Italian applications MI2000A000422 and MI99A001317 filed March 3, 2000 and June 14, 1999, respectively. The entire contents of each of the above-identified applications are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] 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.

[0003] 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.

[0004] The preparation of a sustained, controlled, delayed, extended or anyhow modified release form can be carried out according to different techniques:

[0005] 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.

[0006] 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.

[0007] 3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

[0008] All the procedures listed above suffer, however, from drawbacks and imperfections.

[0009] Inert matrices, for example, generally entail non-linear, but exponential, release of the active ingredient.

[00010] Hydrophilic matrices: have a linear behaviour until a certain fraction of active ingredient has been released, then significantly deviate from linear release.

[00011] 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.

[00012] 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

[0010] The same notion of canalization of an inert matrix is described in U.S. Patent 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 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.

[0011] 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.

[0012] 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

[0013] The invention provides controlled release and taste masking oral pharmaceutical compositions containing as active ingredient budesonide comprising:

[0014] 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;

[0015] b) an amphiphilic matrix;

[0016] c) an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed;

[0017] d) optionally other excipients.

[0018] A particular aspect of the invention consists of controlled release oral compositions containing as active ingredient budesonide comprising:

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