MAIL STOP AF
AMENDMENT AFTER FINAL
EXPEDITED PROCESSING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 13/617,138
Applicant	: Roberto VILLA *et al.*
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AMENDMENT AFTER FINAL

MAIL STOP AF
Director of the United States Patent
and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Office Action dated 6 March 2013, please amend this application as follows:

Amendment to the Specification begins on page 2 of this paper.

Amendments to the Claims begin on page 34 of this paper.

Remarks begin on page 36 of this paper.

Exhibit 1015
ARGENTUM

AMENDMENT TO THE SPECIFICATION

Please amend the specification as follows:

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, now U.S. Patent No. 8,293,273; 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~~ which reissued as U.S. Patent No. RE43,799 from 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:~~

[0019] ~~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;~~

[0020] ~~b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed, preferably by mixing;~~

[0021] ~~c) optionally other excipients.~~

[0022] ~~A further aspect of the invention provides taste masking oral pharmaceutical compositions budesonide containing comprising:~~

[0023] ~~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;~~

[0024] ~~an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;~~

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