

FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER: 9623 V/vmf/as
		U.S. APPEAL NO. (If known, see 37 CFR 1.57) 10/009532
INTERNATIONAL APPLICATION NO.: PCT/EP00/05356	INTERNATIONAL FILING DATE: 09 JUNE 2000 (09.06.00)	PRIORITY DATE CLAIMED: 14 JUNE 1999 (14.06.99)
TITLE OF INVENTION: CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITIONS		
APPLICANT(S) FOR DO/EO/US: Roberto VILLA, Massimo PEDRANI, Mauro AJANI and Lorenzo FOSSATI		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1.	<input checked="" type="checkbox"/>	This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2.	<input type="checkbox"/>	This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3.	<input checked="" type="checkbox"/>	This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4.	<input type="checkbox"/>	A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5.	<input checked="" type="checkbox"/>	A copy of the International Application as filed (35 U.S.C. 371(c)(2))
	a. <input checked="" type="checkbox"/>	is transmitted herewith (required only if not transmitted by the International Bureau).
	b. <input type="checkbox"/>	has been transmitted by the International Bureau. (see attached copy of PCT/IB/308)
	c. <input type="checkbox"/>	is not required, as the application was filed in the United States Receiving Office (RO/US).
6.	<input type="checkbox"/>	A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7.	<input type="checkbox"/>	Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
	a. <input type="checkbox"/>	are transmitted herewith (required only if not transmitted by the International Bureau).
	b. <input type="checkbox"/>	have been transmitted by the International Bureau.
	c. <input type="checkbox"/>	have not been made; however, the time limit for making such amendments has NOT expired.
	d. <input type="checkbox"/>	have not been made and will not be made.
8.	<input type="checkbox"/>	A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9.	<input checked="" type="checkbox"/>	An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10.	<input type="checkbox"/>	A translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
Item 11. to 16. below concern document(s) or information included:		
11.	<input checked="" type="checkbox"/>	An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12.	<input checked="" type="checkbox"/>	An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13.	<input checked="" type="checkbox"/>	A FIRST preliminary amendment.
	<input type="checkbox"/>	A SECOND or SUBSEQUENT preliminary amendment.
14.	<input type="checkbox"/>	A substitute specification.
15.	<input type="checkbox"/>	A change of power of attorney and/or address letter.
16.	<input checked="" type="checkbox"/>	Other items or information: INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT/IPEA/409), INTERNATIONAL SEARCH REPORT (PCT/ISA/210), APPLICATION DATA SHEET, ABSTRACT

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 107009532	INTERNATIONAL APPLICATION NO. PCT/EP00/05356	ATTORNEY'S DOCKET NO. 9623 V/vmf/as
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17. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$ 1,040.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$ 890.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$ 740.00 International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$ 710.00 International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$ 100.00 <p style="text-align: right;">ENTER APPROPRIATE BASIC FEE AMOUNT =</p>	CALCULATIONS PTO USE ONLY																																																							
Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)).	\$ 890.00																																																							
<table border="1" style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="width:20%;">CLAIMS</th> <th style="width:20%;">NUMBER FILED</th> <th style="width:20%;">NUMBER EXTRA</th> <th style="width:20%;">RATE</th> <th style="width:20%;">\$</th> </tr> </thead> <tbody> <tr> <td>Total claims</td> <td>14 - 20 =</td> <td>0</td> <td>X \$18.00</td> <td>\$</td> </tr> <tr> <td>Independent claims</td> <td>1 - 3 =</td> <td>0</td> <td>X \$84.00</td> <td>\$</td> </tr> <tr> <td colspan="3">MULTIPLE DEPENDENT CLAIMS(S) (if applicable)</td> <td>+ \$280.00</td> <td>\$</td> </tr> <tr> <td colspan="4" style="text-align: right;">TOTAL OF ABOVE CALCULATIONS =</td> <td>\$ 890.00</td> </tr> <tr> <td colspan="4">Reduction of 1/2 for filing by small entity, if applicable. Applicant claims Small Entity Status under 37 CFR 1.27</td> <td style="text-align: right;">\$ 445.00</td> </tr> <tr> <td colspan="4" style="text-align: right;">SUBTOTAL =</td> <td>\$ 445.00</td> </tr> <tr> <td colspan="4">Processing fee of \$130 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492(f)).</td> <td style="text-align: right;">\$</td> </tr> <tr> <td colspan="4" style="text-align: right;">TOTAL NATIONAL FEE =</td> <td>\$ 445.00</td> </tr> <tr> <td colspan="4">Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property</td> <td style="text-align: right;">\$ 40.00</td> </tr> <tr> <td colspan="4" style="text-align: right;">TOTAL FEES ENCLOSED =</td> <td>\$ 485.00</td> </tr> </tbody> </table>	CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	Total claims	14 - 20 =	0	X \$18.00	\$	Independent claims	1 - 3 =	0	X \$84.00	\$	MULTIPLE DEPENDENT CLAIMS(S) (if applicable)			+ \$280.00	\$	TOTAL OF ABOVE CALCULATIONS =				\$ 890.00	Reduction of 1/2 for filing by small entity, if applicable. Applicant claims Small Entity Status under 37 CFR 1.27				\$ 445.00	SUBTOTAL =				\$ 445.00	Processing fee of \$130 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	TOTAL NATIONAL FEE =				\$ 445.00	Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$ 40.00	TOTAL FEES ENCLOSED =				\$ 485.00	Amount to be refunded: charged:
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- a. A check in the amount of \$ 485.00 to cover the above fees is enclosed.
- b. Please charge my Deposit Account No. **25-0120** in the amount of \$ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. The Commissioner is hereby authorized to charge any additional fees which may be required by 37 CFR 1.16 and 1.17, or credit any overpayment to Deposit Account No. **25-0120**. A duplicate copy of this sheet is enclosed.

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December 12, 2001

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 Attorney for Applicant
 Registration No. 35,041

CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL
COMPOSITIONS

5 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
10 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
15 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.

20 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

25 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
30 towards aqueous fluids; such property being known as
lipophilia.

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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 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 US 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

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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 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

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