Coated Trimebutine Maleate Tablet

Field of the invention

This invention concerns an improved, coated trimebutine maleate tablet intended for oral administration, and its method of preparation.

In particular, the invention concerns a new tablet which permits administration of a therapeutically effective amount of trimebutine maleate for a biologically rapid or prolonged availability, but, in any case, without producing a persistent bitter effect which, in the end, prejudices the proper observance of the treatment by the patient.

Technological background to the invention

Trimebutine, or 3,4,5-trimethoxybenzoate from 2-dimethylamino-2-phenyl-*n*-butyl, is the first drug known to act on the peripheral encephalinergic receptors, particularly digestive receptors. It is a regulator of the digestive motor functions. Just as it is, or salified by maleic acid, trimebutine is offered in tablet, injectable solution, and suppository form and in powder form for making up a suspension to be taken orally. Marketed internationally, these various pharmaceutical forms are indicated in the treatment of pain linked to functional disorders of the digestive tract and bile ducts, and in the treatment of pain and discomfort connected with intestinal functional disorders.

The orally-administered forms are more particularly suited to ambulatory treatments. These are essentially tablets and also granules or powders which may be intended for preparing suspensions to be taken orally.

Trimebutine maleate is the active ingredient currently used in the preparation of these oral forms with an indicative daily dosage of 300 to 600 mg for adults. This product, obtained by crystallisation in water, dissolves at 105-106°C. Its solubility in water at 25°C is about 1% (p/v),

whereas the basic trimebutine is insoluble in water.

From the chemical point of view, trimebutine is a benzoate-type ester sensitive to agents promoting hydrolysis reactions or those related to them. These agents include notably water and reactive solvents such as the lower alcohols, temperature, light and various catalysts, particularly metal catalysts when they are alkaline or alkaline-earth catalysts. Hydrolysis of trimebutine leads to, among other by-products, the formation of 3,4,5-trimethoxybenzoic acid, the quantitative analysis of which enables an assessment of its chemical stability in various conditions of preservation.

Also maleic acid is heat sensitive through its propensity for isomerisation in fumaric acid whose acidity constant is lower than that of maleic acid. This acid, through salification with trimebutine, leads to trimebutine fumarate with a low solubility in water.

Furthermore, like a number of positively-charged compounds in aqueous solution with pH values close to neutrality, trimebutine maleate, administered orally, induces in the buccal cavity and on the buccal mucous membranes a strong bitterness and lasting astringent sensation which can, in the end, result in poor observance of the treatments for which the product is prescribed. This bitterness is particularly penalising when it is necessary to obtain a rapid therapeutic effect which assumes a biological availability almost immediately as soon as the drug has been swallowed. To illustrate the reality of this problem, one of the two patent medicines in tablet form marketed in France points out that "the tablets must be swallowed without chewing, with a glass of water" ("Vidal" Dictionary of Patent Medicines - 1996 ed.).

At this time, the prior art only mentions some imperfect attempts to overcome the problems exposed, that is to say both to ensure the stability of trimebutine maleate during preparation and preservation of the drugs and to mask or eliminate, in buccal terms, the persistent bitterness caused by the product without delaying its therapeutic effect.

As far as the powder form is concerned, Patent FR 2 468 364 published on 8/5/1981 describes a process for preparing microcapsules containing a pharmaceutically-active compound and whose walls are ethylcellulose, a process carried out in cyclohexane and which brings in a phase-separation inducing agent, preferably of the phospholipid group. For example, it is prepared from trimebutine maleate capsules for which one of the assessed criteria of quality is the absence of bitter taste.

According to this same process carried out in cyclohexane, the patents which follow aim to improve the quality of the microcapsules:

- FR 2 506 613 published on 3/12/1982 describes microcapsules, whose walls are constituted of ethylcellulose and a polymer insoluble in water but soluble in an acid medium, which aim at a rapid release of the product in a gastric medium. The amount of incorporated trimebutine maleate does not exceed 15%, the release of 50% of the product in an artificial gastric medium being obtained after 17 minutes.

- EP 0 076 515 published on 13/4/1983 also concerns rapid-release microcapsules in a gastric medium whose walls are constituted of ethylcellulose and a polymer soluble in water and/or an acid medium. The amount of the product included is at best 12%, of which 50% is released in 10 to 20 minutes.

- EP 0 076 428 also published on 13/4/1983 aims at the same objective as the preceding patents, the walls are constituted of ethylcellulose and a polymer "inflatable" in water. They contain about 10% of active ingredient of which 50% is released in 4 to 25 minutes in an artificial gastric medium.

- EP 0 099 109 published on 25/1/1984 describes a foreshadowed process advantageous in preparing microcapsules in which a particular phase-separation inducing agent intervenes.

It is obvious that through this succession of patents, their applicant aimed at preparing a powder containing trimebutine maleate in the coated state in order to mask its bitterness while attempting

to obtain a rapid release of the active ingredient from the proposed microcapsules. It appears that this aim has been imperfectly achieved, since on the one hand this complex and economically unsatisfactory process makes use of cyclohexane which is an inflammable solvent, difficult to eliminate and, on account of residual solvent, subjected to rigorous standards by the health authorities, and since, on the other hand, it leads to microcapsules which only contain an amount of trimebutine maleate less than 20%, which requires patients to absorb an excessively large amount of medicament, given the recommended daily dosage of 300 to 600 mg of trimebutine maleate, and seeing that they contain an amount of excipients more than four times greater than the active ingredient.

Application JP 80 40 885 published on 13/2/1996 describes a formulation composed of a mixture of granules in which, for those containing trimebutine maleate, the bitter taste is practically eliminated by crystallisation of the active ingredient with a polymer insoluble in water and a hydrophobic salt. For example, granules comprising trimebutine maleate contain 20% of the active ingredient, 3% of insoluble polymer and 5% of a hydrophobic salt, namely magnesium stearate or calcium stearate. No result concerning the speed of release and/or the stability of trimebutine maleate in the granules is mentioned.

As for the trimebutine maleate tablets intended for oral administration, Patent FR 2 640 876 published on 29/06/1990 describes a pharmaceutical composition in the form of a tablet free of coating and containing, as the active ingredient, the maleate of trimethoxy-3,4,5 benzoate from dimethylamino-2-phenyl-2-butanol-1, characterised in that this active ingredient, which represents 35 to 45% by weight of the composition, is dispersed homogeneously in a hydrophilic porous matrix of hydroxypropylmethyl cellulose representing 15 to 20% by weight of the composition which further includes 20 to 25% by weight of a water-soluble diluent and 10 to

20% by weight of tartaric acid.

According to this invention the dissolution kinetic of the active ingredient is, between 30 minutes and 8 hours, similar to zero order, 50% approximately of the product being released after 8 hours.

It should be noted that these tablets, in particular those heavily dosed, may prove difficult to swallow for certain patients, and that, under these conditions, the involuntarily prolonged period of contact in the buccal cavity inevitably causes an unpleasant and persistent bitterness.

Application JP Nº 73574/1990 published on 6/12/1991 aims at a solid preparation very similar to that of Patent FR 2 640 876 and trimebutine maleate tablets intended to be administered orally, in which an organic acid, at the rate of 0.1 to 20 mg for 100 mg of maleate, significantly inhibits the decomposition of the product, a decomposition in which magnesium stearate is partially involved. It is specified that the appropriate acids are tartaric acid or citric acid and that the formulation includes a metallic stearate (magnesium or calcium) as the lubricating agent for the compression.

Description of the invention

This invention, in overcoming the unresolved problems as exposed in the prior art, is a technically simple solution, economically advantageous and beneficial to the patient, which has the objective of a new improved trimebutine maleate tablet intended for oral administration, characterised in that it comprises:

- a centre comprising 30 to 60% of trimebutine maleate, and excipients adapted to the preparation of the said centre and those suited to the stability and release of the active ingredient,
- a water-soluble coating, of transient effectiveness but sufficient to keep the centre from disintegrating and premature release of the active ingredient in a buccal medium.

As described in this specification, in its main aspect, the invention concerns a new tablet for

orally administering an effective therapeutic amount of trimebutine maleate whose biological availability can be made rapidly or can be prolonged but, whatever the case, producing in the buccal cavity no persistent bitterness which, with use, causes a repulsive attitude in the patient. These tablets display a resistance and remarkable physical stability which makes them suitable for the most diverse packaging (blister packs, in bulk in bottles ...) in testing preservation conditions (temperature, humidity ...).

Equally one important aspect concerns the remarkable chemical stability of trimebutine maleate in this form of tablets, even stored in severe conditions, which provides patients a certain sense of security and therapeutic benefit. In another aspect, the invention is directed at the process of making the tablets.

Another aspect of the invention concerns a composition suitable for the preparation of the tablet centres, characterised in that the quantitative and qualitative matching of its main constituents allows a rapid or prolonged release of the active ingredient to be obtained.

Generally the coating of the tablets provides advantages both for their industrial production and for their use by the patient alike. Thus, with regard to the production aspect, the coated forms are acknowledged to be less sensitive to mechanical erosion, therefore generate less dust and, for this reason, reduce the inter-medicament contamination on the premises; also it is recognised that coating favours the primary packaging, in particular blister packs, of tablets. With regard to use by the patients, the satin-like or glossy texture imparted by the film-forming mixture of the coating avoids adherence of the bare tablet to the buccal mucous membrane and makes swallowing easier.

As well as these known advantages, the improvements given by the tablets of the invention are elaborated upon in the rest of this specification and illustrated by tests of the release of the active ingredient and tests of physical and chemical stability, compared with two marketed patent medicines.

In the widest sense of the invention, the tablets are characterised in that their centres comprise, by weight 30 to 60% of trimebutine maleate, and, as excipients 15 to 45% of one or more diluting agents, 2.5 to 25% of one or more binding agents, 0.5 to 25% of one or more acid-forming agents, optionally 1 to 5% of one or more disintegrating agents, and technically useful agents, namely 0.5 to 5% of a flow behaviour agent and 0.25 to 2.5% of a lubricant and characterised in that the said centres are coated with a film representing 1 to 5% by weight of the said tablet, the film's composition comprising one or more water-soluble film-forming agents, one or more opacifiers, and, optionally, one or more plasticisers.

More precisely the composition of a centre consists of:

- at the rate of 20 to 40%, one or more diluting agents selected from cellulose in microcrystalline or powder form, mannitol, starch and more especially lactose, particularly hydrous lactose, which is the preferred diluting agent.
- at the rate of 2.5 to 25%, one or more binding agents selected from microcrystalline cellulose, pharmaceutically-acceptable quality gelatin, methylcellulose, pregelatinised starch. Povidone, pregelatinised cornstarch and hydroxypropylmethyl cellulose with a viscosity between 2.5 and 15,000 mPa.s are preferred. Especially for the centres for which rapid disintegration is desired, a mixture is used representing 5 to 10% of the tablet and composed of 5 to 10 parts of cornstarch and 0.5 to 2 parts of hydroxypropylmethyl cellulose with a viscosity between 2.5 and 17.5 mPa.s, whereas for the centres for which a prolonged release of the active ingredient is desired, a mixture is used - at the rate of 15 to 20% of the tablet - and is composed of 5 to 15 parts of hydroxypropylmethyl cellulose whose viscosity is between 1,500 and 15,000 mPa.s and 0.5 to 1 part of povidone. In a particularly preferred way, hydroxypropylmethyl cellulose with a viscosity of 5.2 to 7.0 mPa.s is used for rapid-disintegrating centres and hydroxypropylmethyl cellulose with a viscosity of 4,000 mPa.s is used for prolonged-release centres.

- the acid-forming agent is selected from the pharmaceutically-acceptable organic acids, known for their metal sequestration properties and/or having a stabilising effect on the active ingredient and/or enabling the creation of an acid environment favourable to the release of the active ingredient of hydrophilic centres aiming at a prolonged release. These acids are citric acid and tartaric acid, which, in the centres for which a prolonged release of trimebutine maleate is desired, are used preferably at the rate of 10 to 20% especially with tartaric acid which is preferred.

- the flow behaviour agent is anhydrous or hydrous silicon dioxide which is used at the rate of 0.75 to 2.5%.

- the lubricant is selected from the metallic salts of stearic acid to the exclusion of other agents usually proposed for this effect. The lubricant is thus selected from calcium or magnesium stearate. The latter is preferred in concentrations of 0.5 to 1.5% and more especially 1%.

- the disintegrating agent, which is optional, is selected from crospovidone (cross-linked polyvidone), the sodium salt of cross-linked carboxymethyl cellulose, also called "sodium croscarmellose" and carboxymethyl starch which is preferred. The optional nature of this agent corresponds to the possible requirement for rapid release of the active ingredient which is obtained by the rapid disintegration of the centres after passing from the bucco-pharyngeal sphere. To this end, for the tablets known as "immediate release" tablets, sodium carboxymethyl starch is used at the rate of 1 to 5% and preferably 2% to obtain the expected disintegration.

And, with regard to the coating film, this is essentially constituted of: a water-soluble film-forming agent selected from the acrylic polymers or cellulosed polymers such as hydroxypropylmethyl cellulose with a viscosity between 2.5 and 17.5 mPa.s, methylcellulose, ethylcellulose, hydroxypropylcellulose, and a filler substance enabling a better adherence of the film to the centre, such as crystalline lactose or cellulose. The opacifiers and/or additive

colouring agents are selected from the iron oxides or titanium dioxide. The plasticisers which can be used are selected from the macrogols with an average molecular weight of 3000 to 6000, propylene glycol, glycerin or polyoxyl 40 stearate. To implement the coating of the centres, according to the invention the compounds can be used mixed in solution or in suspension in water or in pharmaceutically-acceptable solvents such as ethanol, acetone or their mixtures with water. However, preference is given to a mixture comprising an aqueous suspension of hydroxypropylmethyl cellulose whose viscosity lies between 2.5 and 17.5 mPa.s and titanium dioxide or even a mixture comprising a hydroxypropylmethyl cellulose whose viscosity lies between 2.5 and 17.5 mPa.s, microcrystalline lactose or cellulose, polyethylene glycol with a molecular weight of 4000 or polyoxyl 40 stearate and titanium dioxide in aqueous suspension. Especially preferred are mixtures in which hydroxypropylmethyl cellulose has a viscosity of 5.2 to 7.0 mPa.s; particularly suitable mixtures are marketed by the Colorcon company under the OPADRY® brand or by the Seppic company under the SEPIFILM® brand which, at a rate of 1.5 to 3% by weight relative to the weight of the centre and especially at a rate of 2%, enable a film to be obtained with a transitory resistance in a bucco-pharyngeal medium which allows the tablet to be administered without any effect of bitterness while preserving the biological availability of the active ingredient in the release conditions selected for the latter. Moreover, the coating produced by the film in the conditions of the invention perfectly observes the recessed or embossed engraving of the centres, the engraving being indicative of the active ingredient and its quantitative analysis and which, during the coating operation with unsuitable compositions, can be either filled up, eroded and in any case become illegible.

In a particularly preferred case, the invention aims at tablets whose centesimal compositions are as follows:

Tablet A with rapid disintegration, known as immediate release form: "FLI"

i) composition for centres of 200 & 400 mg

- trimebutine maleate	50.00%
- monohydric lactose	36.00%
- cornstarch	7.00%
- hydroxypropylmethyl cellulose (6 mPa.s)	1.00%
- sodium carboxymethyl starch	2.00%
- tartaric acid	1.0%
- silica gel	2.00%
- magnesium stearate	1.00%

ii) coating 2.00% of the weight of the centre with a composition comprising hydroxypropylmethyl cellulose (6 mPa.s), lactose, polyethylene glycol 4000 and titanium dioxide, or alternatively hydroxypropylmethyl cellulose (6 mPa.s), microcrystalline cellulose, polyoxyl 40 stearate and titanium dioxide.

Tablet B known as prolonged release: "FLP"

i) composition for centres of 747.00 & 508.00 mg

- trimebutine maleate	39.37%
- monohydric lactose	23.6 %
- hydroxypropylmethyl cellulose (4000 mPa.s)	15.75%
- tartaric acid	15.75%
- providone	1.57%
- silica gel	1.00%
- magnesium stearate	1.00%

ii) coating 2.00% of the weight of the centre with a composition comprising

hydroxypropylmethyl cellulose (6 mPa.s) and titanium dioxide or alternatively hydroxypropylmethyl cellulose (6 mPa.s), lactose, polyethylene glycol 4000 and titanium dioxide.

With regard to the process for manufacturing the tablets according to the invention, the process consists in a first stage in preparing an appropriate composition, then subjecting it to compression to obtain the centres which are coated later.

Thus, the implementation of the process for preparing the tablets known as "FLI", whose preferred constituents have been described previously for Tablets A, consists:

i) in preparing the composition

- in a powder mixer or fluidised bed device, mixing the trimebutine maleate, monohydric lactose, pregelatinised cornstarch, hydroxypropylmethyl cellulose and half of the carboxymethyl starch, then granulating the homogeneous mixture with the tartaric acid in aqueous solution and grading the moist granules.
- drying the granules in a fluidised bed or ventilated oven at a temperature of 45 to 60°C, grading them on a 1 to 1.5 mm aperture sieve, then mixing them in a powder mixer with the hydroxypropylmethyl cellulose, silica gel and magnesium stearate.

ii) in preparing the centres by compressing the granules on a rotary tablet press with appropriate size punches to obtain centres with a mass equivalent to 200 or 400 mg, dosed respectively with 100 to 200 mg of trimebutine maleate and whose hardness is 50 to 70 N.

iii) in coating the centres in a turbomixer with the coating suspension at a temperature between 35 and 45 °C and in conditions such that the coating covers the centres uniformly at a rate of an amount of 4 mg for the 200 mg centres and 8 mg for the 400 mg centres.

Implementation of the process for preparing Tablets B known as "FLP" is little different from that set out previously and consists:

i) in preparing the composition

- in a powder mixer or fluidised bed device, mixing the trimebutine maleate, monohydric lactose, and tartaric acid then granulating the homogeneous mixture with an aqueous or ethanolic solution of providone and grading the moist granules.

- drying the granules in a fluidised bed or ventilated oven at 60°C, then grading them on a 1 to 1.5 mm aperture sieve, then mixing them in a powder mixer with the second half of the carboxymethyl starch, silica gel and magnesium stearate.

ii) in preparing the centres by compressing the granules on a rotary tablet press with appropriate size punches to obtain centres with a mass equivalent to 747 or 508 mg, dosed respectively with 300 and 200 mg of trimebutine maleate and whose hardness is 80 to 200 N.

iii) in coating the centres in a turbomixer with the coating suspension at a temperature between 35 and 45 °C and in conditions such that the coating covers the centres uniformly at a rate of an amount of 15 mg for the 747 mg centres and 10 mg for the 508 mg centres.

Prepared like this, the coated tablets are then packaged in blister packs, high density polypropylene bottles, etc ...

The invention is illustrated in a non-limiting way by the following examples.

Example 1: <u>rapid-disintegrating coated tablets dosed with 100 mg of trimebutine maleate - "FLI" form</u>

Introduced into a spray and swirl powder mixer are:

- 10.400 kg of trimebutine maleate,
- 7.488 kg of monohydric lactose,
- 1.450 kg of pregelatinised cornstarch,
- 0.208 kg of sodium carboxymethyl starch,

- 0.208 kg of hydroxypropylmethyl cellulose (6 mPa.s).

The homogeneous mixture of the constituents is produced by agitation for 3 minutes, then, in the same apparatus by using the tool matched to the granulation, the mixture is moistened by a solution of 0.208 kg of tartaric acid in solution in 2.7 l of water.

The granules are graded moist on the rotary grader then dried on a fluidised bed at 50°C until the residual moisture is less than 1%.

The granules are then graded on a rapid filter of 1.5 mm aperture size then introduced into a container-type powder mixer. Then added are:

- 0.208 kg of carboxymethyl starch,
- 0.416 kg of silica gel,
- 0.208 kg of magnesium stearate.

The whole is mixed for 20 minutes at slow speed (5 to 10 rpm) then subjected to compression on a rotary compression press fitted with 8 mm diameter punches.

The centres obtained have the following characteristics:

- average mass 200 mg ± 15 mg
- average hardness 60 N ± 10 N
- brittleness < 1%
- disintegration time in water at 37°C: maximum 8 minutes.

The centres are then coated in a turbomixer (for example in a machine of the "ultra coater aeromatic S_2 type) by spraying an aqueous suspension containing methylhydroxypropyl cellulose (6 mPa.s), hydrous lactose, titanium dioxide and polyethylene glycol 4000. In the above-mentioned type of machine the operating conditions are as follows:

- air inlet temperature: 50°C,
- coating suspension admission rate: 30 g/minute,
- spraying pressure: 2 bars,

to obtain, at a temperature of 35 to 45°C, a homogeneous coating of 4 mg by compression whose average final mass is 204 mg ± 15.3 mg and whose unit composition is as follows:

- trimebutine maleate	100.0 mg
- monohydric lactose	72.0 mg
- pregelatinised cornstarch	14.0 mg
- hydroxypropylmethyl cellulose	2.0 mg
- sodium carboxymethyl starch	4.0 mg
- tartaric acid	2.0 mg
- silica gel	4.0 mg
- magnesium stearate	2.0 mg
- mixture of coating agents	4.0 mg

among which hydroxypropylmethyl cellulose (6 mPa.s) 0.93 mg, hydrous lactose 1.4 mg, titanium dioxide 0.87 mg and polyethylene glycol 4000 0.80 mg.

The primary packaging of these tablets is made in thermoformed sheets (polyvinyl aluminium chloride).

An identical operating method is used to prepare the "FLI" tablets dosed with 200 mg of trimebutine maleate. The modification applied consists in fitting the rotary compression press with appropriate punches to obtain centres with an average mass of 400 mg, which, in the conditions of the example, is produced with punches whose diameter is 11 mm. These centres are then coated with a mixture of coating agents, at a rate of 8 mg per centre so as to obtain finished tablets with an average mass of 408 mg.

Example 2: prolonged-release coated tablets dosed with 300 mg of trimebutine maleate - "FLP" form

Into an "Aeromatic"-type fluidised bed device are introduced:

- 10.500 kg of trimebutine maleate,
- 2.100 kg of monohydric lactose,
- 4.200 kg of tartaric acid;

after homogenising, 2.000 kg of a 21% (p/v) aqueous solution of povidone is progressively added and the mixing is continued for 16 minutes. The grain obtained is dried at 60°C until the residual solvation, determined in the heat balance, is less than 0.6%.

The granulate is then mixed for 2 minutes then subjected to compression on a rotary compression press. The centres obtained have the following characteristics:

- average mass 747 mg ± 30 mg
- average hardness 180 N ± 20 N
- brittleness < 1%.

The centres are then coated in a turbomixer as described in Example 1 with an aqueous suspension containing hydroxypropylmethyl cellulose (6 mPa.s), and titanium dioxide to obtain a homogeneous coating of 15 mg per tablet whose average final mass is 762 mg ± 30 mg and whose composition is as follows:

- trimebutine maleate	300.0 mg
- monohydric lactose	180.0 mg
- tartaric acid	120.0 mg
- polyvidone	12.0 mg
- hydroxypropylmethyl cellulose	120.0 mg
- silica gel	7.5 mg
- magnesium stearate	7.5 mg

- mixture of coating agents 15.0 mg

among which hydroxypropylmethyl cellulose 6 mPa.s 11.5 mg and titanium dioxide 3.5 mg.

The tablets are packaged in thermoformed sheets or in bottles depending on their use and storage conditions.

An alternative mode of operation consists in equipping the rotary compression press with punches suited to the preparation of centres whose average mass is 508.0 mg dosed with 200.0 mg of trimebutine maleate. The centres are coated with the mixture of coating agents at the rate of 10.0 mg per centre to obtain the finished tablets whose average mass is 518.0 mg.

Tests

The tests performed include:

- the study of the physical and chemical stability of the rapid-release or prolonged-release coated tablets of the invention,
- the comparative study of the rapid release- coated tablets of the invention with marketed tablets.

Apart from the assessment of appearance, the tests concerning physical criteria were carried out in accordance with protocols adapted from the European Pharmacopoeia, which are the tests of:

- disintegration (Ph. Eur. V.5.1.1),
- dissolution (Ph. Eur. V.5.4.1),
- brittleness (Ph. Eur. V.5.8.2.-1),
- hardness (Ph. Eur. V.5.8.3.-1).

With regard to the studies of chemical stability of trimebutine maleate, these were determined by the quantitative analysis of 3,4,5-trimethoxybenzioc acid which is representative of the hydrolysis of the active ingredient. This quantitative analysis is performed by high-pressure liquid chromatography (CLHP - Ph. Eur. V.6.20.4) with a 125 mm column with a Lichrospher 60 RP select B Merck type support and by carrying out elution with a phosphate pH 3.6 - acetonitrile

buffer solution, spectrophotometric detection being carried out at 220 nm.

- stability tests

In packaging in thermoformed sheets (PVC - aluminium) or in polypropylene bottles, the tested "FLI" and "FLP" coated tablets has been preserved for 6 months in ovens at 40°C ± 4°C, in a dry atmosphere or relative humidity (RH) of 75% ± 5%. The results of these tests are quoted in the following tables.

1) Stability of FLI tablets

The tests were carried out after 6 months preservation of the tablets at 40°C ± 4°C in an atmosphere with a relative humidity of 75% ± 5%.

The criteria adopted for the test are:

- appearance, disintegration time, hardness, crumbling and the active ingredient dissolution test with regard to physical stability,

- quantitative analysis of the TMBA with regard to the chemical stability of the active ingredient.

	T_0	$T_{6\ months}$ 40°C + 75% rel. hum.
Physical stability		
- appearance	white	off-white
- hardness	79 N	82 N
- crumbling	1.27 %	0.69%
- disintegration time	7 to 9 mn	10 to 12 mn
- dissolution test 10 mn	25.0 %	20.7%
- dissolution test 20 mn	100.3 %	96.9%
- dissolution test 30 mn	100.9%	101.8%
Chemical stability		
- % TMBA	0.01%	0.10%

2) Stability of FLP tablets

The tests were performed after 6 months preservation of the tablets at 40°C ± 4°C in an anhydrous material and in an atmosphere with a relative humidity of 75% ± 5%.

The criteria adopted for the test are:

- appearance and the dissolution test for physical stability,

- quantitative analysis of the TMBA for chemical stability of the active ingredient.

		T_0	$T_{6\ months}$	
			40°C	40°C + 75% rel. hum.
Physical stability				
- appearance		white	off-white	off-white
- dissolution	1h	7.6%	7.3%	
	4h	25.8%	27.7%	
	8h	49.0%	54.8%	
Chemical stability				
- % TMBA		0.09%	0.10%	0.15%

These tests, which were carried out in severe preservation conditions, are convincing evidence of the excellent stability of the tablets of the invention.

With regard to the "FLI" tablets:

- the physical stability proves to be outstanding, particularly when considering the significant criterion of the objective aimed at by the invention, which is to avoid the premature disintegration of the tablet and, consequently, the dissolution of the active ingredient. In fact, on these points, after 6 months a slight increase in the disintegration time (about 3 minutes) is observed, which corresponds to a slight decline in the speed of dissolution of the trimebutine maleate,

- the chemical stability is also considered satisfactory.

The formation of 0.09% of TMBA corresponds to the ratios of molecular weights to the

decomposition of $\frac{0.09 \times 503.5}{212.2}$ = 0.21% of trimebutine maleate.

(TMBA - Mol. Wt. = 212.2; trimebutine maleate - Mol. Wt. = 503.5)

With regard to the "FLP" tablets:

- the physical stability is outstanding, when considering the criterion of dissolution which is essential for the prolonged-release forms,

- the chemical stability is also good when considering that the formation of 0.06% TMBA corresponds to the decomposition of 0.14% of trimebutine maleate.

- comparative tests

To demonstrate noteworthy improvements brought about by the coated form according to the invention, comparative tests were carried out between the tablets obtained from Example 1 and marketed tablets dosed with 100.0 mg of trimebutine maleate.

As far as the latter are concerned, the qualitative information on the excipients of the two patent medicines appear in the "Vidal" Dictionary of Patent Medicines:

- Tablets "D": lactose, D-mannitol, sucrose, polyethylene glycol 6000, magnesium stearate, gelatin, wheat starch, silica gel.

- Tablets "T": lactose, hypromellose, croscarmellose, magnesium stearate.

The tablets in Example 1 were compared with the "D" tablets and/or "T" tablets with regard to first, the release of the active ingredient and second, their chemical stability after preservation at 40°C - 75% relative humidity for 6 months with regard to the hydrolysis of the trimebutine maleate determined by quantitative analysis of 3,4,5-trimethoxy benzoic acid (TMBA).

The results are given in the following tables:

	Ex. 1	Tab. "D"	Tab. "T"
% dissolution			
- 10 mn	23.0%	26.0%	83.3%
- 20 mn	101.2%	50.4%	98.7%
- 30 mn	101.7%	69.2%	98.6%
- 45 mn	-	92.9%	
- 60 mn	-	98.0%	

Comparative study of dissolution

	Tests at 6 months 40°C - 75% rel. hum.		
	Ex. 1	Tab. "D"	Tab. "T"
- % TMBA	0.10%	0.45%	0.70%
- % decomp. of active ingredient (*)	0.23%	1.06%	1.66%

Comparative study of stability

(*) relative % decomposition calculated relative to the molecular weights of TMBA (212.2) and trimebutine maleate (503.5) and disregarding the TMBA present at T_0.

These tests are convincing evidence of the improvements provided by the coated tablet according to the invention:

- the dissolution study proved the transitory effectiveness of the coating which allowed almost the whole of the active ingredient to be released between 10 and 20 minutes, whereas for the "D" tablets the entire release is obtained only after 60 minutes, and for the "T" tablets the release is practically complete by 10 minutes. These results demonstrate that the "D" tablets, in order to avoid the buccal bitterness, releases the active ingredient only slowly and in an excessively retarded manner whereas, conversely, the "T" tablets release the trimebutine maleate excessively

rapidly, which results in the occurrence of the persistent buccal bitterness.

- the study of chemical stability demonstrates that, taken as a whole, the decomposition of the trimebutine maleate is respectively 4 and 6 times greater in the "D" and "T" tablets than in the tablets of the invention according to Example 1.

Claims

1.) Trimebutine maleate coated tablet intended for oral administration, characterised in that it comprises:

- a centre consisting of 30 to 60% of trimebutine maleate, and excipients adapted to the preparation of the said centre and those suited to the stability and release of the active ingredient,
- a water-soluble coating, of transient effectiveness but sufficient to keep the centre from disintegrating and premature release of the active ingredient in a buccal medium.

2.) Coated tablet according to Claim 1, characterised in that its centre comprises, in weight, 30 to 60% of trimebutine maleate, and, as excipients 15 to 45% of one or more diluting agents, 2.5 to 25% of one or more binding agents, 0.5 to 25% of one or more acid-forming agents, optionally 1 to 5% of one or more disintegrating agents, and technically useful agents, namely 0.5 to 5% of a flow behaviour agent and 0.25 to 2.5% of a lubricant.

3.) Coated tablet according to Claims 1 and 2, characterised in that the acid-forming agent is tartaric acid at the rate of 0.5 to 2% in the centres for rapid release of the trimebutine maleate, and at the rate of 10 to 20% in the centres for prolonged release.

4.) Coated tablet according to Claim 1, characterised in that the coating represents 1 to 5% by weight of the matrix and in that its composition comprises one or more water-soluble film-forming agents, one or more opacifiers, and, optionally, one or more plasticisers.

5.) Coated tablet according to Claims 1 and 4, characterised in that the coating is selected from a mixture of hydroxypropylmethyl cellulose with viscosity of between 2.5 and 17.5 mPa.s and titanium dioxide and a mixture composed of hydroxypropylmethyl cellulose with viscosity of between 2.5 and 17.5 mPa.s, microcrystalline lactose or cellulose, polyethylene glycol with a molecular weight 4000 or polyoxyl 40 stearate and titanium dioxide.

* C L M S *

6.) Rapid-disintegrating coated tablet whose centesimal compositions for centres of 200 and 400 mg is:

i) centres

- trimebutine maleate	50.00%
- monohydric lactose	36.00%
- cornstarch	7.00%
- hydroxypropylmethyl cellulose (6 mPa.s)	1.00%
- sodium carboxymethyl starch	2.00%
- tartaric acid	1.0%
- silica gel	2.00%
- magnesium stearate	1.00%

ii) coating 2.00% of the weight of the centre with a composition comprising hydroxypropylmethyl cellulose (6 mPa.s), lactose, polyethylene glycol 4000 and titanium dioxide, or alternatively hydroxypropylmethyl cellulose (6 mPa.s), microcrystalline cellulose, polyoxyl 40 stearate and titanium dioxide.

7.) Prolonged-release coated tablet whose centesimal composition for centres of 747.00 & 508.00 mg is:

i) centres

- trimebutine maleate	39.37%
- monohydric lactose	23.6 %
- hydroxypropylmethyl cellulose (4000 mPa.s)	15.75%
- tartaric acid	15.75%
- providone	1.57%
- silica gel	1.00%

- magnesium stearate 1.00%

ii) coating 2.00% of the weight of the centre with a composition comprising hydroxypropylmethyl cellulose (6 mPa.s) and titanium dioxide or alternatively hydroxypropylmethyl cellulose (6 mPa.s), lactose, polyethylene glycol 4000 and titanium dioxide.

8.) Process for preparing coated tablets which consists:

i) in preparing the mixture of the constituents of the centres

- by mixing the trimebutine maleate and excipients in a powder mixer or a fluidised bed mixing device then by granulating the homogeneous mixture with the acid-forming agent in aqueous solution and grading the moist granules,

- by drying the granules on a fluidised bed or in a ventilated oven at 60°C, then grading them and mixing them in a powder mixer with the silica gel and magnesium stearate.

ii) in preparing the centres by compressing the granules on a rotary tablet press with appropriate size punches,

ii) in coating the centres in a turbomixer with the coating suspension at a temperature between 35 and 45 °C and in conditions such that the coating covers the centres uniformly at a rate of an amount of 2% of their weight.