SUSTAINED-RELEASE PHARMACEUTICAL FORMULATIONS CONTAINING MIZOLASTINE

The present invention relates to novel sustained-release pharmaceutical formulations containing 2-[[1-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]piperid-4-yl]methylamino]-pyrimidin-4-ol or 2-[[1-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]piperid-4-yl]methylamino]-pyrimidine-4(1H)-one, or mizolastine, as active principle.

Mizolastine is described in European patent EP 0,217,700.

Mizolastine binds to the H_1 histamine receptor and inhibits the degranulation of mastocytes in vitro and in vivo. It can thus be used for the treatment of respiratory, cutaneous or ocular allergies and various allergic manifestations.

During the oral administration of immediate-release formulations containing mizolastine, undesirable sedative effects have been observed which are associated with the existence of a high peak in the plasma.

Consequently, it was necessary to find formulations for an oral administration which have a profile of release of the active principle such that it is possible to obtain a lower peak in the plasma without decreasing the bioavailability.

The Applicant Company has based its research

of such formulations on the study of the kinetics of dissolution of mizolastine. The reason for this is that mizolastine is a weak base (pK 5.6) which is sparingly soluble in water (13 mg/l at neutral pH) but much more soluble at acidic pH (11 g/l at pH 3); the first gelatin capsules released 100 % of mizolastine over 30 minutes in a dissolution medium at pH 2 whereas only 40 % were dissolved at pH 6.8.

Moreover, the release of mizolastine from the sustained-release pharmaceutical form according to the invention did not need to be influenced by the differences in pH in the gastrointestinal tract.

The aim of the present invention is to propose formulations containing mizolastine whose dissolution profile is as follows:

- about 30 to 70 % of mizolastine dissolved in 1 hour,
- 100 % of mizolastine dissolved in 3 to 5 hours, and
- pH-independent profile.

The Applicant Company has shown that tablets containing a core formed of a sustained-release tablet containing mizolastine combined with a fatty matrix and with an organic acid, the said tablet being coated to prevent degradation of the product by light, are entirely suitable.

The tablets according to the invention contain from 1 mg to 25 mg of mizolastine. These doses

correspond to concentrations of from 0.5 % to 12 % by weight of mizolastine.

The fatty matrix is made with hydrogenated castor oil or with hydrogenated lecithins or long-chain fatty acids, for example C_{12}-C_{28} long chain fatty acids such as behenic acid, or triglycerides esterified with medium-chain fatty acids, for example C_8-C_{18} fatty acids.

The organic acid preferably having a pK of 2 or more is chosen from maleic, tartaric, malic, fumaric, lactic, citric, adipic and succinic acids in the form of racemates or isomers. According to the invention, the acid particularly preferred is L-tartaric acid.

The weight ratio between the mizolastine and the organic acid should be between 0.3 and 1. With L-tartaric acid, this ratio is preferably equal to 0.5.

The tablets are prepared by granulation using the active principle, the agent constituting the fatty matrix, the organic acid and other excipients such as, for example, lactose, mannitol and sugars or similar sugar-alcohols, microcrystalline cellulose, starch, calcium phosphates and sulphates, polyvidone, and substituted celluloses such as hydroxypropyl-cellulose, hydroxypropylmethylcellulose or methylcellulose.

The granulation may be carried out in a wet phase, for example in the presence of water or alcohol, or may be performed by fusion or by compacting. The

granulation step may optionally be left out and the tablets prepared by direct tableting of the mixture of mizolastine and the excipients.

Anhydrous colloidal silica and magnesium stearate are added to the granules obtained and the mixture is tableted. The tablets are then covered with a coating film by spraying them with a coating solution in a machine with a fluidized-air bed or in a coating turbine.

The example which follows illustrates the invention without limiting it:

Tablet

	% (weight)
mizolastine	4.8
hydrogenated castor oil	12.0
lactose	60.0
microcrystalline cellulose	9.6
L-tartaric acid	9.6
polyvidone	2.9
anhydrous colloidal silica	0.2
magnesium stearate	0.9
purified water	Q.S.
Total	100.0

Coating

methylhydroxypropylcellulose	74.0
titanium dioxide (E171)	18.5

propylene glycol	7.5
purified water	Q.S.
Total	100.0

The dissolution profile obtained with a formulation according to the invention is given in Figure 1.

This profile gives about 50 % of product dissolved in 1 hour, 100 % of product dissolved in 3 to 5 hours, and it is independent of the pH.

The dissolution profile obtained with a formulation identical to that of the invention but containing no L-tartaric acid is given in Figure 2.

The plasma kinetics of a pharmaceutical form according to the invention containing 10 mg of mizolastine were studied in a healthy volunteer after a single oral administration, compared with a standard immediate-release gelatin capsule containing 10 mg of mizolastine.

Table 1 presents the kinetic parameters and Figure 3 the curves of the plasma kinetics, obtained respectively with each formulation; the plasma kinetics obtained with the pharmaceutical form according to the invention makes it possible to prevent any peak in the plasma without losing bioavailability.

The plasma kinetics of a pharmaceutical form according to the invention were also studied in comparison with the same formulation without L-tartaric

acid.

The study was performed on twelve healthy volunteers after a single oral administration of a tablet according to the invention containing 10 mg of mizolastine or the same tablet without L-tartaric acid.

Table 2 shows that the bioavailability of the formulation containing no L-tartaric acid represents only 43 % of that observed with the formulation according to the invention containing L-tartaric acid. The values of Cmax and the AUC values (0-∞) are respectively 1.5 and 2 times as high for the formulation containing L-tartaric acid as for that not containing any.

In addition, for the formulation with L-tartaric acid, the min.-max. variation indices are much lower, which suggests great uniformity in the release.

The results altogether show that the formulations according to the invention have:

- a pH-independent dissolution profile,
- an *in vivo* release which prevents any peak in the plasma,
- a bioavailability which is not decreased relative to an immediate-release formulation,
- lower variability of the plasma kinetics results.

CLAIMS

1. Sustained-release pharmaceutical formulation containing mizolastine, characterized in that it contains a core formed of a sustained-release tablet containing mizolastine combined with a fatty matrix and with an organic acid, the said tablet being coated.

2. Sustained-release pharmaceutical formulation according to Claim 1, characterized in that the weight ratio between the mizolastine and the organic acid is between 0.3 and 1.

3. Sustained-release pharmaceutical formulation according to either of Claims 1 and 2, characterized in that the fatty matrix is made with hydrogenated castor oil or with hydrogenated lecithins or long-chain fatty acids or triglycerides esterified with medium-chain fatty acids.

4. Sustained-release pharmaceutical formulation according to any one of Claims 1 to 3, characterized in that the organic acid is chosen from maleic, tartaric, malic, fumaric, lactic, citric, adipic and succinic acids in the form of racemates or isomers.

5. Sustained-release pharmaceutical formulation according to any one of Claims 1 to 4, characterized in that the organic acid is L-tartaric acid.

6. Sustained-release pharmaceutical formulation according to Claim 5, characterized in that the ratio between the mizolastine and the L-tartaric acid is 0.5.

7. Formulation according to any one of Claims 1 to 6, characterized in that it contains from 1 to 25 mg of mizolastine.

Figure 1

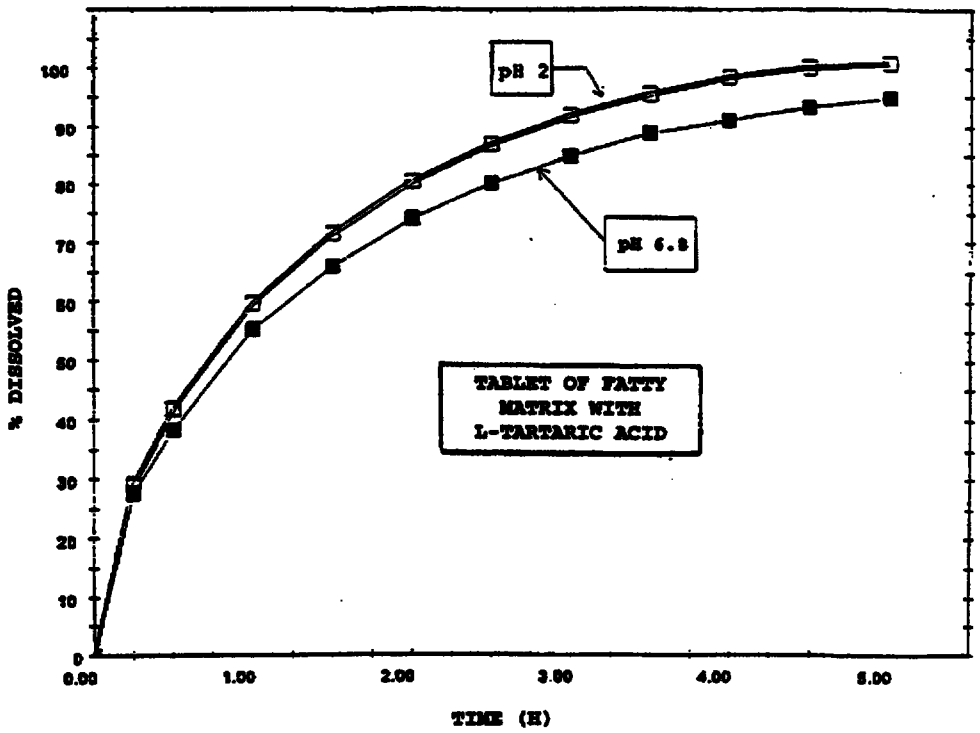


Figure 2

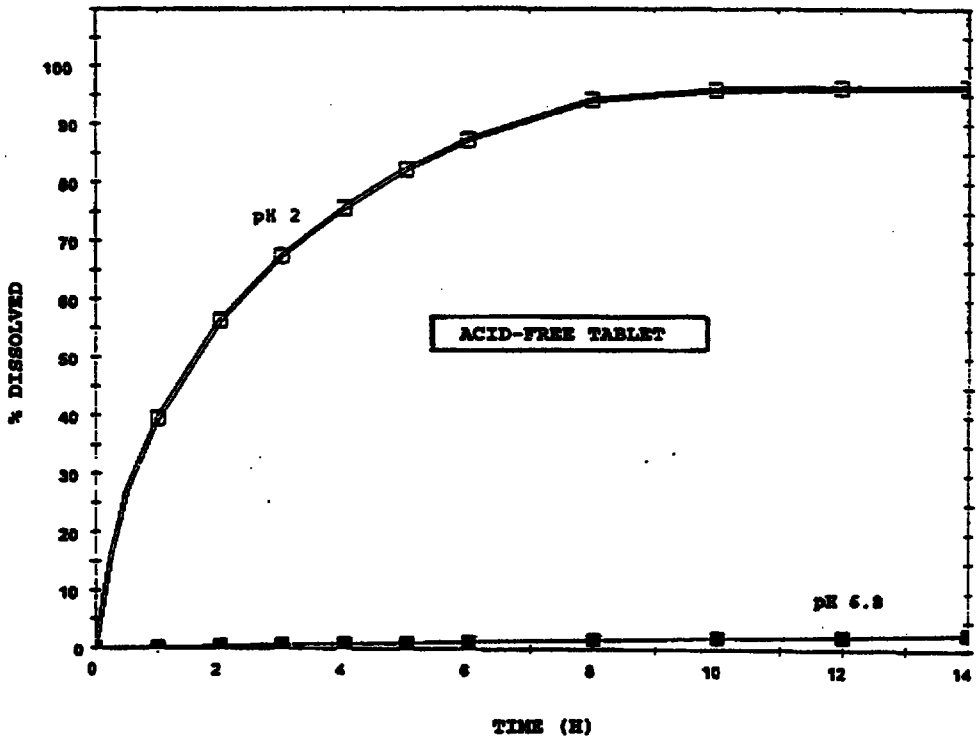


Table 1

Formulation	Tmax (h)	Cmax (ng/ml)	t1/2β (h)	AUC(0-∞) ($ng.ml^{-1}.h$)	Frel
Gelatin capsule	0.9	398.4±22.7	14.8±1.5	1481±96	
Min-Max	0.5-1.5	202-529	6.7±33.1	1092-2717	
Tablet	1.4	234.2±13.7	14.5±1.2	1406.1±119	0.962
Min-Max	0.5-2.5	154-393	6.7-26.4	775-2458	
Statistical comparison	NS	p<0.001	NS	NS	

Figure 3

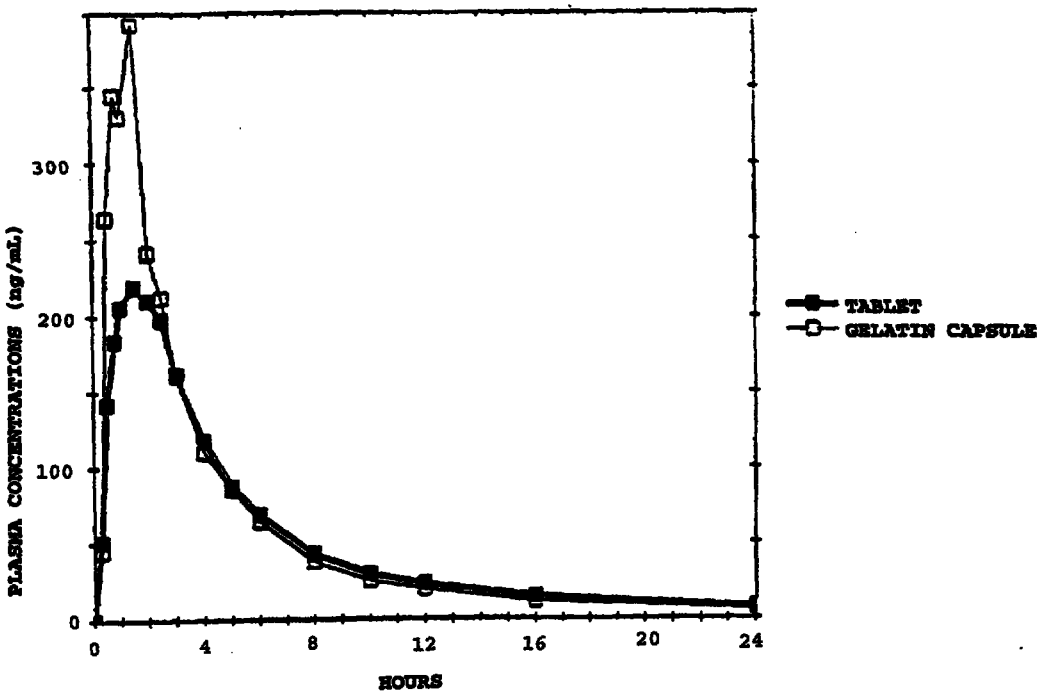

PLASMA CONCENTRATIONS (ng/mL)
300
200
100
0
0
4
8
12
16
20
24
HOURS
TABLET
GELATIN CAPSULE

Table 2

Formulation	Tmax (h)	Cmax (ng/mL)	t1/2β (h)	AUC(0-t) $ng.ml^{-1}.h$	AUC(0-∞) $ng.ml^{-1}.h$	Frel
With L-tartaric acid	1.00	243.7±12.7	13.1±1.2	1347±117	1444±125	
Min-Max	0.75-2.5	166.5-314.1	5.9±19.4	734-1878	773-2011	
Without L-tartaric acid	0.75	147.0±28.8	12.9±1.1	601±134	635±139	0.43±0.08
Min-Max	0.5-2.5	4.5-285.4	5.1-17.6	27-1347	38-1397	0.03-0.87
Statistical comparison	NS	p<0.05	NS	p<0.01	p<0.01	

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(71) Applicant (for all designated States except US): SYNTHELABO [FR/FR]; 22, avenue Galilée, F-92350 Le Plessis-Robinson (FR).

(72) Inventors; and
(75) Inventors/Applicants (US only): Maryvonne CHARIOT [FR/FR]; 22, ruelle des Néfliers, F-91620 La Ville-du-Bois (FR). Gareth LEWIS [GB/FR]; 39, avenue de Paris, F-91410 Dourdan (FR). Jean MONTEL [FR/FR]; 3, rue Le Val-Sablon, F-78400 Chatou (FR).

(74) Representative: Elisabeth THOURET-LEMAITRE; Synthélabo, 22, avenue Galilée, F-92350 Le Plessis-Robinson (FR).

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(57) Abstract

A slow-release pharmaceutical formulation containing mizolastin and characterised in that it comprises a core consisting of a slow-release tablet comprising mizolastin combined with a fatty matrix and an organic acid, said tablet being coated, is disclosed.

(57) Abrégé

Formulation pharmaceutique à libération prolongée contenant de la mizolastine, caractérisée en ce qu'elle comporte un noyau formé d'un comprimé à libération prolongée comportant de la mizolastine associée à une matrice grasse et à un acide organique, ledit comprimé étant enrobé.