



166166

WO 99/38511

- 1 -

PCT/FR98/01783

"Gastroprotected microgranules of omeprazole,
production process and pharmaceutical preparations"

The present invention relates to a
5 pharmaceutical formulation of omeprazole in the form of
gastroprotected microgranules having an improved
stability over time.

The present invention additionally applies to
the process for the manufacture of the said
10 microgranules and to the pharmaceutical preparations
containing them.

Omeprazole or 5-methoxy-2-[[[4-methoxy-3,5-di-
methyl-2-pyridinyl)methyl]sulphonyl]-1-benzimidazole is
known as a powerful inhibitor of acidic gastrointestinal
15 secretion (Swedish Patent No. 78 04231) and can be used
in the treatment of gastric and duodenal ulcers.

It is also known that omeprazole readily
degrades in acidic medium and in neutral medium. The
degradation half-life of omeprazole is ten minutes at a
20 pH of less than 4, eighteen hours at a pH equal to 6.5
and approximately 300 days at a pH equal to 11.

For this reason, pharmaceutical dosage forms of
omeprazole for oral administration are gastroprotected
so that the active principle reaches the small intestine
25 without being degraded.

During long-term storage under normal conditions
of use (temperature of 25°C and degree of humidity of
the order of 40-75%), it has been observed that
conventional formulations are not stable over time. The
30 degradation of the omeprazole, the appearance of harmful
degradation products and colouring of the formulation
have been observed.

This is because the stability of omeprazole is
also affected by moisture, heat, the presence of organic
35 solvents, even in the form of traces, and, to a lesser
extent, light. Organic solvents are generally used in
the process for the manufacture of omeprazole
formulations, which it is desired to avoid for
ecological reasons.



G00002

- 2 -

In order to improve the duration of stability on storage of gastroprotected formulations comprising omeprazole or an alkaline salt of omeprazole, the active principle is often combined with an excipient, such as:

- 5 • an alkaline substance (see Patent Application EP-247,983), for example a sodium, potassium, calcium or aluminium salt of an organic acid, such as phosphoric acid, carbonic acid or citric acid,
- an antiacid substance, for example an aluminium,
10 magnesium or calcium oxide or hydroxide,
- a pharmaceutically acceptable organic buffer substance, such as a basic amino acid or one of their salts, in particular trihydroxymethylamino-methane,
- 15 • an inert substance, such as mannitol (see Patent Application of EP-646,006) or titanium dioxide (see Patent Application WO 96/37 195),
- an agent which dehydrates, during the final packaging of the formulation.

20 However, it has been observed that the stability of the formulations of the prior art is unsatisfactory and the aim of the present invention is to provide a gastroprotected formulation of omeprazole microgranules which is stable to coloration, the stability to long
25 term storage of which is improved and which additionally exhibits the desired therapeutic properties, that is to say a degree of resistance to dissolution in acidic medium and rapid solubility in neutral medium.

 The object of the present invention is thus to
30 provide gastroprotected microgranules of omeprazole which exhibit dissolution profiles corresponding to the targeted therapeutic application and which are advantageously stable over time.

 The present invention relates to a novel gastro-
35 protected formulation of omeprazole comprising at least one hydrophobic substance chosen in order to increase the stability of the active principle while obtaining the desired dissolution profile. The Applicant Company

- 3 -

has in particular optimized the composition of such a formulation by selecting combinations of several hydrophobic substances in order to achieve the objective of the present invention.

The microgranules of omeprazole which are the subject-matter of the present invention are advantageously devoid:

- of alkaline compounds in the form of salts,
- of ionic surface-active agents, such as the lauryl sulphate commonly used to stabilize omeprazole, and
- of traces of organic solvents.

The microgranules of omeprazole according to the invention each comprise an active layer comprising the active principle and an external gastroprotective layer comprising a gastroprotection agent and are characterized in that they are devoid of alkaline compounds in the form of salts and that the active layer comprises a hydrophobic substance.

Hydrophobic substances will be chosen which do not react chemically with omeprazole, which can be easily employed during formulation, which are compatible with the excipients used and which make it possible to obtain the dissolution and release profiles desired for the targeted therapeutic application.

In the active layer, the hydrophobic substance preferably represents between 5 and 40% by weight of the omeprazole.

In a preferred embodiment, the active layer comprising the omeprazole is advantageously coated with at least one protective layer.

This protective layer can comprise a diluent substance or a coating agent in combination with a hydrophobic plasticizer.

The gastroprotection agent can be combined, in the external gastroprotective layer, with a hydrophobic agent preferably chosen from glycerides.

According to a particularly advantageous embodiment, the microgranules according to the invention use a combination of different hydrophobic agents which makes

- 4 -

it possible to improve the stability of the formulation.

According to a preferred embodiment, the microgranules according to the invention comprise:

- a layer of active principle comprising omeprazole,
5 a binder chosen from any pharmaceutically acceptable binder, a hydrophobic substance and a substance which dissolves the active principle,
- a first protective layer comprising one or more pharmaceutically acceptable diluent substances and
10 a binder chosen from any pharmaceutically acceptable binder,
- a second hydrophobic protective layer comprising a coating agent and a hydrophobic plasticizer,
- a gastroprotective layer comprising an enteric
15 film-forming agent, a plasticizer and a hydrophobic substance.

The layer of active principle advantageously comprises a hydrophobic substance of the fatty substance type advantageously chosen from silicone oils: it
20 preferably represents between 5 and 40% of the weight of active principle.

A non-ionic surfactant, preferably chosen from polysorbates (Montanox 80° or Montane 20-60°), is also included in this layer in a proportion of 5 to 15% with
25 respect to the weight of active principle.

The active layer advantageously comprises a binder chosen from pharmaceutically acceptable binders, in this case hydroxypropylmethylcellulose, the proportion by mass of which represents 30 to 50% with
30 respect to the weight of active principle.

The first protective layer advantageously comprises an inert substance chosen particularly from pharmaceutically acceptable diluents, including mannitol (which is non-hygroscopic), in a proportion by mass of
35 100 to 300% and preferably 200% of the weight of the active principle.

This layer also comprises a binder chosen from pharmaceutically acceptable binders, advantageously

- 5 -

hydroxypropylmethylcellulose, in a proportion of 10 to 30% and preferably 20% of the weight of mannitol.

It is optionally possible to include, in this protective layer, a lubricant chosen from pharmaceuti-
5 cally acceptable lubricants, in this case talc (which is non-hygroscopic), in a proportion of 0 to 100% of the weight of the active principle.

The second protective layer is composed of a water-soluble coating agent chosen from pharmaceutically
10 acceptable film-forming agents and advantageously hydroxypropylmethylcellulose, in a proportion of 1 to 10%, preferably 5%, of the weight of microgranules obtained after coating on the first protective layer.

Use will advantageously be made, in the second
15 protective layer, of a hydrophobic plasticizer, such as Myvacet®, in a proportion of 10 to 30% of the dry varnish of the coating agent used.

Use will optionally be made of a lubricating agent chosen from pharmaceutically acceptable
20 lubricants, advantageously talc (which is non-hygroscopic), in a proportion of 10 to 50%, preferably 15%, of the dry varnish of the coating agent used.

The external gastroprotective layer comprises a gastroprotective film-forming agent, advantageously a
25 methacrylic acid copolymer, such as Eudragit L30D®, in a proportion of 15 to 30%, preferably 20%, of polymer, on a dry basis, with respect to the mass of microgranules which is treated.

There will advantageously be included, with the
30 gastroprotective film-forming agent, one or more hydrophobic substances chosen from the waxes and oils often used in the pharmaceutical industry, preferably Gélucire 50-13®, in a proportion of 5 to 20% of the dry varnish of the film-forming agent used.

35 Use can optionally be made, for the external gastroprotective layer, of a plasticizer chosen from pharmaceutically acceptable plasticizers, preferably triethyl citrate, representing from 5 to 20%, advanta-

- 6 -

geously 10%, of the weight of dry varnish of the film-forming agent used.

Use will optionally be made, in order to reinforce the resistance to moisture of the gastroprotective layer, of a lubricating agent chosen from pharmaceutically acceptable lubricants, advantageously talc.

According to a preferred embodiment of the present invention, the active layer is coated on a neutral core composed, for example, of sucrose and starch, the diameter of which is between 700 and 900 microns.

The microgranules according to the invention will preferably have a particle size of between 0.5 and 3 mm, more preferably between 0.7 and 2 mm.

Another subject-matter of the present invention is a process for the preparation of the microgranules according to the invention. This process is characterized in that it is carried out in aqueous medium, without using any organic solvent.

The microgranules described in the present invention will be obtained by using any appliance appropriate for the preparation and the coating of microgranules which is well known to a person skilled in the art and, in particular, appliances of conventional turbomixer, perforated turbomixer or fluidized air bed type.

According to a preferred embodiment, the microgranules according to the invention are obtained by coating on a neutral core, preferably in a fluidized air bed, by successively spraying:

- an aqueous suspension of omeprazole and a hydrophobic substance,
- optionally an aqueous suspension of a diluent substance, and/or
- an aqueous suspension of a coating agent and a hydrophobic plasticizer, and
- an aqueous suspension of the gastroprotection

agent, also known as enteric film-forming agent.

According to a very particularly valued embodiment, the microgranules according to the invention are coated on a neutral core, in a fluidized air bed, by successively spraying:

- an aqueous suspension of omeprazole and a silicone oil,
- an aqueous suspension of mannitol,
- an aqueous suspension of hydroxypropylcellulose, and
- an aqueous suspension of the gastroprotection agent.

Each spraying stage is advantageously followed by sieving and drying at a temperature below the melting temperature of each of the compounds forming part of the composition of the microgranules at the said stage.

The microgranules obtained according to this process advantageously comprise less than 1.5%, preferably 0.5%, by weight of water.

Finally, a subject-matter of the present invention is the pharmaceutical preparations comprising the microgranules according to the invention which are capable of being obtained by the process described above; these preparations will advantageously be in the form of gelatin capsules comprising 5 to 60 mg approximately of omeprazole.

Other characteristics and advantages of the present invention will become apparent in the light of the examples and figures hereinbelow.

Figure 1 represents the in vitro dissolution curve at pH 6.8 of gelatin capsules according to the invention (curve a) compared with that of an oral omeprazole formulation of the prior art (curve b).

Figure 2 represents the in vivo dissolution curve of gelatin capsules according to the invention (curve 1) compared with that of an oral omeprazole formulation of the prior art (curves 2).

Figure 3 represents the change over time of the

- 8 -

mean plasma concentration of omeprazole in 10 patients, to whom a formulation of the invention was administered (curve A1), and in the same 10 patients, to whom a formulation of the prior art was administered (curve B).

5 . Figure 4 represents the change over time of the mean plasma concentration of omeprazole in 10 patients, to whom a formulation of the invention was administered (curve A2), and in the same 10 patients, to whom a formulation of the prior art was administered (curve C).

10

- 9 -

EXAMPLE 1

Microgranules are prepared in a fluidized air bed device of Ohlman type.

5 a) Coating the [lacuna] principle

A suspension of the active principle is prepared which has the following composition.

Composition of the suspension of active principle	% by mass
Omeprazole	14.9
Pharmacoat 603°	5.9
Dimethicone	4.2
Polysorbate 80°	1.5
Purified water	73.5

10 The purified water is stirred and the Pharmacoat 603° (manufactured by Seppic), the Polysorbate 80° (manufactured by Seppic), the Dimethicone (manufactured by Lambert and Rivi re) and the omeprazole are successively added.

15 Stirring of the suspension is maintained throughout the coating of the Neutres 20° (manufactured by NP Pharm) placed in the fluidized air bed.

The coated Neutres° are subsequently sieved and dried for four hours at approximately 50 C.

20

b) Pharmacoat°/Mannitol precoating

A precoating suspension is prepared consisting of 4% by weight of Pharmacoat 603°, 20% by weight of Mannitol 25° (both manufactured by Roquette) and 76% of
25 purified water.

The coated and dried Neutres obtained above are sprayed with this precoating suspension.

The precoated Neutres are subsequently sieved and then dried for one to four hours at approximately
30 50 C.

- 10 -

c) Pharmacoat®/Myvacet® precoating

A precoating suspension is prepared with the following composition.

Composition of the precoating suspension	% by mass
Pharmacoat 603®	7.14
Myvacet 0.45®	1.79
Talc	1.79
Purified water	89.28

5

This precoating stage is carried out under the same conditions as the Pharmacoat®/Mannitol precoating stage.

During stages a), b) and c), the temperature of the granules is maintained between 26 and 28°C during the spraying of the suspension.

10

d) Eudragit L30D®/Gélucire® coating

A coating suspension is prepared with the following composition:

15

Composition of the coating suspension	% by mass
Eudragit L30D®	54.64
Triethyl citrate	1.64
Gélucire 5013®	1.64
Purified water	42.08

molten Gélucire® (manufactured by Gattefosse) being added at 50°C.

20

The coated microgranules are subsequently sieved and dried at approximately 45°C for four hours and then lubricated with talc.

The losses on drying of the microgranules are of the order of 0.5 to 1% after fifteen minutes at 95°C, at the end of each of stages a) to d).

25

- 11 -

EXAMPLE 2

Microgranules are prepared according to the process of Example 1, in order to obtain the following formulations A and B.

5

Composition	Percentage by mass	
	Formulation A	Formulation B
Neutres 20°	47.5	36.2
Omeprazole	7.9	9.0
Pharmacoat 630°	9.1	11.2
Dimethicone	0.8	0.9
Polysorbate 80°	0.8	0.9
Mannitol 25	12.0	20.3
Myvacet 9.45V	0.9	0.9
Talc	0.9	1.2
Eudragit L30D°	16.6	16.2
Triethyl citrate	1.6	1.6
Gélucire 5013°	1.6	1.6

	Formulation A	Formulation B
Content (mg/g)	71	88
Gastroresistance test (Percentage by mass)		
after 2 h at pH 1.2	1.8	1.4
then for 30 min at pH 6.8	88.3	86

In accordance with the European Pharmacopoeia, the in vitro dissolution tests are carried out, with a device with a paddle rotating at a rate of 100 revolutions/minute, in 750 ml of water at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and pH = 1.2, to which is added, after two hours, after having carried out the standard, 250 ml of an aqueous solution of Na_3PO_4 at pH = 12.5, in order to obtain 1 l of a solution at pH = 6.8.

15

- 12 -

Stability studies

The stability of the unpackaged formulation A over time under actual storage conditions (i.e. at 25°C and 40% relative humidity) is evaluated.

5

Formulation A	t = 0	t = 11 months
Gastroresistance test (%)		
after 2 h at pH 1.2	4.6	1.4
then for 30 min at pH 6.8	96.3	94.1
Content of impurities (%)	0.4	0.4
Colour	off white	off white

The microgranules A and B prepared in Example 2 are packaged in gelatin capsules of size 2, respectively recorded as G_A and G_B.

10 A first study is carried out under accelerated ageing conditions, according to a standardized ICH test (at 40°C and 75% relative humidity).

The stability tests as a function of time on the gelatin capsules G_A and G_B are carried out by placing the gelatin
15 capsules in opaque polyethylene bottles.

The impurities are quantitatively determined by U.V. spectrometry after separation by high performance liquid chromatography.

The gastroresistance tests are carried out under
20 the same conditions as in Example 2 and must verify the following standard in order to be judged positive:

10% or less after two hours at pH 1.2
and more than 75% after thirty minutes at pH 6.8.

25

The quantitative determination of active principle and the water content are respectively carried out according to the standards USP <905> and USP <921>.

The stability results of the gelatin capsules G_A
30 and G_B under accelerated ageing condition are summarized respectively in Tables 1 and 2.

- 13 -

TABLE 1

G_A	$t = 0$	1 month	2 months	3 months
Quantitative determination (mg/gelatin capsule)	14	14.2	14.2	11.8
Gastroresistance test (%)				
after 2 h at pH 1.2	4.6	0.0	2.0	3.3
then for 30 min at pH 6.8	96.3	90.2	86.3	94.0
Water content (%)	1.4	2.0	1.8	1.9
Content of impurities (%)	0.4	1.0	2.7	10.2
Colours	off white	off white	grey	grey

TABLE 2

5

G_A	$t = 0$	1 month	2 months
Quantitative determination (mg/gelatin capsule)	20	19.7	19.9
Gastroresistance test (%)			
after 2 h at pH 1.2	2	2.4	2.5
then for 30 min at pH 6.8	92.4	91.9	92.4
Water content (%)	0.8	1.4	1.1
Content of impurities (%)	0.3	4.5	4.8
Colour	off white	off white	off white and grey highlights

- 14 -

A comparative study on the stability of the microgranules G_x and of a formulation of the prior art is subsequently carried out, still under accelerated ageing conditions.

5 Table 3 shows the increased stability of the microgranules according to the present invention with respect to a formulation of the prior art sold by the company Astra under the trade name Mopral® (Patent EP-247,983).

10

TABLE 3

	t = 0	1 month	2 months	3 months
Content of impurities (%)				
Mopral®	-	1.06	22.6	38.17
G _x	0.4	1.0	2.7	10.2
Colours				
Mopral®	-	brown	brown	brown
G _x	off white	off white	grey	grey

CLINICAL TRIALS

15 These trials are aimed at confirming that the formulations according to the invention do not cause a loss in bioavailability.

20 • A first study is carried out by comparing the bio-availability parameters of a formulation according to the invention, recorded as A1, and of a formulation of the prior art, recorded as B, sold under the trade name Losec® by the company Astra.

25 This randomized study is carried out on 10 patients, to whom is administered a single dose of 20 mg of microgranules according to the invention. The plasma concentration of omeprazole is monitored during the eight hours following administration.

30

- 15 -

After a resting period of 7 days, these same ten patients receive a single dose of 20 mg of a formulation of the [lacuna] art B. In the same way, the plasma concentration of omeprazole is measured regularly during the eight hours following administration.

The change in the mean plasma concentration of omeprazole (measured with respect to the 10 patients), calculated for A1 and then for B, are represented in Figure 3.

Table 4 gives the mean value of the main bioavailability parameters corresponding to the two curves A1 and B.

TABLE 4

Treatment	AUC _{0-t} (ng/ml)	AUC _{inf} (ng/ml)	C _{max} (ng/ml)	T _{max} (h)	K _{el}	T _{1/2} (h)
A1	544.7	618.6	336.3	2.68	0.097	0.76
Coefficient of variation	(48%)	(42%)	(37%)	(63%)	(31%)	(29%)
B	517.5	554.1	291.1	2.26	1.00	0.75
Coefficient of variation	(57%)	(55%)	(42%)	(44%)	(29%)	(32%)
A1/B ratio	98%	94%	83%	-	-	-

20

- A second study is carried out under the same conditions as above by administering a formulation according to the invention, recorded as A2, and then a formulation of the prior art, recorded as C, sold under the trade name Prilosec® by the company Merck.

25

The change over time in the mean plasma concentration of omeprazole in the 10 patients, measured for A2 and C, is represented in Figure 4.

- 16 -

Table 5 gives the mean value of the main bioavailability parameters corresponding to the two curves A2 and C.

5

TABLE 5

Treatment	AUC _{0-t} (ng/ml)	AUC _{inf} (ng/ml)	C _{max} (ng/ml)	T _{max} (h)	K _{el}	T _{1/2} (h)
A2	423.2	431.9	274.6	2.38	1.11	0.63
Coefficient of variation	(48%)	(56%)	(51%)	(46%)	(13%)	(14%)
C	429.0	459.8	283.6	1.95	1.07	0.67
Coefficient of variation	(41%)	(40%)	(51%)	(50%)	(21%)	(25%)
A2/C ratio	117%	112%	107%	-	-	-

- 17 -

CLAIMS

1. Omeprazole microgranules, each comprising an active layer comprising the active principle and an external gastroprotective layer comprising a gastroprotection agent, characterized in that they are devoid of alkaline compounds in the form of salts and that the active layer comprises a hydrophobic substance.
2. Microgranules according to Claim 1, characterized in that the active layer comprises a hydrophobic substance which represents 5 to 40% by weight of [lacuna] omeprazole.
3. Microgranules according to Claim 1 or 2, characterized in that the active layer is coated with at least one protective layer.
4. Microgranules according to one of Claims 1 to 3, characterized in that the protective layer comprises a diluent substance or a coating agent in combination with a hydrophobic plasticizer.
5. Microgranules according to one of Claims 1 to 4, characterized in that, in the external gastroprotective layer, a hydrophobic agent is used in combination with the gastroprotection agent.
6. Microgranules according to one of Claims 1 to 5, characterized in that each microgranule comprises
 - a layer of active principle comprising omeprazole, a binder chosen from any pharmaceutically acceptable binder, a hydrophobic substance and a substance which dissolves the active principle,
 - a first protective layer comprising one or more pharmaceutically acceptable diluent substances and a binder,
 - a second hydrophobic protective layer comprising a coating agent and a hydrophobic plasticizer,
 - a gastroprotective layer comprising an enteric film-forming agent, a plasticizer and a hydrophobic substance.

- 18 -

silicone oils.

8. Microgranules according to Claim 6 or 7, characterized in that the solubilizing substance is a non-ionic surfactant chosen from polysorbates.

5 9. Microgranules according to one of Claims 6 to 8, characterized in that the binder is hydroxypropylmethylcellulose.

10 10. Microgranules according to one of Claims 6 to 9, characterized in that the first protective layer comprises mannitol as diluent substance.

11. Microgranules according to one of Claims 6 to 10, characterized in that the second protective layer is composed of a coating agent, such as hydroxypropylmethylcellulose, and of a hydrophobic
15 plasticizer, such as Myvacet®.

12. Microgranules according to one of Claims 6 to 11, characterized in that the hydrophobic substance comprised within the gastroprotective layer is chosen from glycerides.

20 13. Microgranules according to one of the preceding claims, characterized in that the active layer is coated on a neutral core and in that the particle size of the microgranules is between 0.5 and 3 mm.

14. Process for the preparation of the microgranules
25 according to one of the preceding claims, characterized in that it is carried out in aqueous medium.

15. Process according to Claim 14, characterized in that a coating operation is carried out in a fluidized air bed.

30 16. Pharmaceutical preparations comprising the microgranules according to one of Claims 1 to 13, or obtained according to the process of either of Claims 14 and 15, comprising 5 to 60 mg approximately of omeprazole.