Abstract:

The present invention describes pharmaceutical formulations suitable for oral administration of esomeprazole and methods of preparation to obtain tablets of the MUPS type of adequate hardness with minimum applied compression force. The present invention relates in particular to pharmaceutical formulations manufactured by production of micro granules containing esomeprazole magnesium dihydrate, which are made resistant to the gastric environment and then compressed, with tableting excipients granulated with water, with applied compression force less than normal for the purpose of obtaining formulations that are stable and resistant to the gastric environment, in the form of MUPS tablets having suitable hardness and low friability.
ORAL PHARMACEUTICAL FORMULATIONS OF ESOMEPRAZOLE IN THE FORM OF MUPS (MULTI UNIT PELLETS SYSTEM) TABLETS

Field of the invention

The present invention relates to the field of formulations of pharmaceutical compositions; in particular it relates to tablets of the MUPS type for oral administration of esomeprazole, and the method of preparation thereof.

Prior art

Esomeprazole belongs to the class of proton pump inhibitors (PPI): drugs containing active ingredients discovered relatively recently, which have proved very effective in treating various gastrointestinal pathologies by reducing the acid secretion of the stomach.

They are drugs that are normally well tolerated, with relatively short plasma half-life but with long time of action through irreversible inhibition of the enzyme H⁺/K⁺ATPase that regulates the production of hydrochloric acid by cells in the wall of the stomach.

In the preparation of formulations suitable for oral administration of esomeprazole there is the problem of stabilization of the active ingredient, which is absorbed in the intestine but is susceptible to degradation in an acid environment.

The addition of alkaline substances and/or "inert" coating layers, applied on the pellets, as well as formation of one or more enteric coating layers, are repeatedly mentioned in the literature for preventing inactivation of the medicinal product in the gastric environment and for guaranteeing stable formulations.

The enteric-coated tablets obtained by the conventional technique have long residence times in the stomach, sometimes unpredictable: there is an increased risk of degradation of the active ingredient, due to the residence time in the stomach and to microinfiltrations in the enteric coating.

In tablets or capsules of the MUPS (Multi Unit Pellet System) type, in contrast, the residence time in the stomach is short because the tablets or capsules disintegrate, releasing enteric-coated pellets having a diameter in the range 0.5-2.0 mm, which therefore pass through the stomach without stopping.

In the tablet compression step, in order to obtain adequate hardness for tablet handling, it is generally necessary to use forces normally above 10-12 kN; however,
even these minimal forces can damage the enteric coating of the pellets of approx. 10%, consequently causing degradation of a similar percentage of the product. The need to achieve the foregoing thus necessitates using particular formulations of pellets or a minimum compression force, with the risk of not obtaining sufficient hardness, so as not to damage the enteric coating of the pellets during compression.

WO96/01623 describes tablets of the MUPS type, containing esomeprazole, in which, to avoid the aforementioned problems of compression, the pellets were coated with an enteric coating that contains a plasticizer in amounts from 20 to 50 wt.%, relative to the weight of the enteric coating. Such a large amount of plasticizer endows the pellets with mechanical resistance to the pressure applied during compression, such as to preserve the enteric characteristics of the pellets.

There are many patents for the preparation of pharmaceutical formulations of the MUPS type containing esomeprazole magnesium dihydrate, which can be classified essentially on the basis of the procedure for preparation of the pellets: some patents envisage the preparation of an initial core by stratification of the active ingredient, others by extrusion and spheronization. The prepared cores are isolated with neutral polymers to protect the active ingredient and are made resistant to the gastric environment by the use of various types of films. Among the various patents, we may mention: WO 2006/002077 A2 and WO 2005/034924 A1, although these describe capsules, not tablets. In the aforementioned patents the active ingredient is preferably mixed with alkaline substances to protect the active ingredient from acidic materials and environments. The cores are isolated by applying neutral polymers characterized by low solubility owing to their high viscosity: it is therefore necessary to use dilute solutions, leading to lengthening of the covering times, made worse by the actual adhesiveness of the film. The concentrations used must be between 2 and 5% otherwise the viscosity becomes so great that spraying of the solutions is not possible.

Despite numerous studies in this area, attempting to overcome the aforementioned problem, to date, none of the proposed solutions has proved completely satisfactory and there is therefore an obvious interest in being able to provide pharmaceutical formulations and methods for obtaining them that are able to solve such problems.

**Summary of the invention**

It was discovered, surprisingly, that by compressing enteric microgranules containing esomeprazole with a wet granulate of tableting excipients, at a pressure much lower...
than that generally employed for preparation of tablets, it is possible to obtain tablets of the MUPS type of suitable hardness and friability for the subsequent operations of film coating and packaging.

The present invention thus solves the aforementioned problem by means of a method for preparation of tablets of the MUPS (Multi Unit Pellet System) type comprising esomeprazole, said method comprising the following steps:

(i) preparation of enteric microgranules (pellets) containing esomeprazole;
(ii) granulation of inert tableting excipients with water to obtain a wet granulate with a water content of 6-15 wt.% relative to said excipients; in which said excipients include cellulose;
(iii) preparation of a mixture comprising enteric microgranules obtained from step (i) and the wet granulate obtained from step (ii);
(iv) compression of the mixture obtained from step (iii) with a compression force equal to 1.8-2.5 kN with lubricated punches.

The granulated excipients are mixed, wet as obtained without prior drying, with the enteric-coated pellets previously produced. What distinguishes the present invention from other pharmaceutical formulations of the MUPS type containing esomeprazole magnesium dihydrate already on the market is the use of a much lower compression force, so that the enteric coating of the pellets is not damaged during compression. In fact, the tablets obtained disintegrate when in contact with the fluids and release the protected granules that they contain. When the tablets obtained by the aforementioned method were submitted to release tests in aqueous solutions of 0.1 M HCl it was observed that, in a preferred embodiment, less than 0.3 wt.% of the esomeprazole that they contain is released in two hours; this confirms that the enteric microgranules preserve their characteristics and are not damaged during compression.

The presence of a water content of approx. 10% in the wet granulate of tableting excipients surprisingly makes it possible to obtain tablets having high hardness and low friability while applying a minimal compression force equal to approx. 2kN. The tablets obtained by the aforementioned method have suitable hardness (above 15kp) and friability for withstanding the usual subsequent steps of film coating and packaging.

The tablets can then be coated with ordinary excipients for film coating in an aqueous medium. During film coating the tablets lose the water added in the step of
granulation of the tabletting excipients. The finished tablets thus produced display, surprisingly, a further increase in hardness at the end of the film coating cycle. In one aspect, the present invention also relates to enteric microgranules containing esomeprazole that are particularly simple and convenient to be prepared and which, even if they do not possess particularly high mechanical strength and must not be submitted to high pressures during compression, can be used particularly advantageously in the aforementioned method; said microgranules each comprising:

(a) an inert core;
(b) a layer containing esomeprazole applied on said inert core;
(c) an isolating layer consisting of mannitol, said isolating layer being applied on layer (b);
(d) an external coating consisting of a gastroresistant film;

said microgranules preferably having an average diameter between 500 and 800 \( \mu \text{m} \);

said layer (b) containing esomeprazole does not contain alkaline substances;
said coating layer (d) can also contain plasticizers but in amounts such as not to endow said coating with sufficient mechanical strength to preserve enteric characteristics during dry compression.

The isolating layer (c) constituted of mannitol, applied simply in aqueous solution, makes it possible to obtain pellets with very fast production times and with excellent results. With the same operating conditions with respect to the neutral polymers used in the aforementioned patents, there is an approximately five-fold decrease in production times.

The aforementioned microgranules can be used, as well as for preparation of tablets of the MUPS type according to the method of the present invention, for the preparation of capsules filled with said microgranules.

Detailed description of the invention

The term "tabletting excipients" means the inert additives, known and mentioned in the various pharmacopoeias, which are generally added to active ingredients, or to granules containing them, to facilitate their compression to tablets; in particular, for preparation of tablets of the MUPS type, disintegrating tabletting excipients are used, for example microcrystalline cellulose, carboxymethyl starch, croscarmellose, crospovidone, pregelatinized starch and others.
Preferably, for the purposes of the present invention, the esomeprazole is esomeprazole magnesium dihydrate.
Preferably the pellets according to the present invention have an average diameter between 500 and 800 \( \mu \text{m} \).

The pellets according to the invention are prepared by fluidized bed technology. Preferably the layer containing the active ingredient further comprises usual excipients, preferably polysorbate, povidone or PEG and mixtures thereof. The layer of active ingredient does not comprise alkalinizing substances. The layer containing the active ingredient is applied on the inert (neutral) cores using an aqueous suspension of the components of the layer in which the active ingredient is contained at 15-25 wt.\%, more preferably at approx. 20\%. In said aqueous suspension, the active ingredient is contained in larger amounts than is known in the prior art, in which suspensions are used at 6-10 wt.\% of active ingredient. It has now been discovered that it is also possible to work with higher concentrations (up to 15-25 wt.\%) when said aqueous suspension is prepared and maintained at a temperature not above 20°C, preferably between 10 and 20°C; in fact, by carrying out homogenization of the suspension at this temperature, it is possible to prevent gelation thereof and make the spraying operation possible.

The isolating layer of mannitol is preferably applied by means of fluidized bed technology using a solution of mannitol in water preferably at a concentration by weight below 50\%, more preferably at 10-30\%. Said solution of mannitol is preferably at pH 9-10, said pH preferably being obtained by adding a 1N solution of NaOH.

The pellets according to the invention are made resistant to the gastric environment using suitable films for this purpose, known and referred to in the various pharmacopoeias; among these, preferably the following can be used: Eudragit L100-55, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate, cellulose acetate phthalate, hydroxypropylmethylcellulose succinate, polyvinyl acetate. The enteric coating can further comprise other usual excipients, for example glycercy1 monostearate, triethyl citrate, talc, paraffin and mixtures thereof. However, any plasticizers present are in amounts below 25 wt.% relative to the enteric polymers. The aforementioned amount of plasticizer is not sufficient to endow the pellets with the necessary mechanical strength in dry compression. The pellets are
preserved, however, when compressed with wet granulate of tableting excipients according to the method of the present invention.

The pellets according to the invention or others selected for example from those known in the prior art are mixed with the tableting excipients and then compressed. It is convenient for the purposes of the present method to use the microgranules according to the present invention because they are easier to prepare while maintaining the desired enteric characteristics and release at neutral or slightly alkaline pH.

Preferably the granulate of the tableting excipients comprises cellulose and preferably further comprises an alditol of general formula $H[CH(OH)]_nH$ where $n$ is between 5 and 12. Said tableting excipients are advantageously constituted of cellulose or of mixtures of cellulose and an alditol of general formula $H[CH(OH)]_nH$ where $n$ is between 5 and 12, preferably selected from mannitol, lactitol, isomalt, maltitol, sorbitol or xylitol. The aforementioned mixture of cellulose+alditol preferably comprises 70-90 wt.% of cellulose and the remaining 10-30% of alditol. The aforementioned cellulose+alditol mixture is preferably obtained by co-spray drying.

In the method according to the invention the tableting excipients are granulated with addition of water, to obtain a wet granulate with a water content preferably of 7-13%, more preferably 9-11% (based on the weight of the excipients). The water content was evaluated by testing for weight loss on drying. The water used for preparation of the granulate of tableting excipients is preferably acidified beforehand to pH 3-5, preferably using hydrochloric acid.

The wet granulate is mixed with the enteric-coated pellets previously produced without carrying out drying. The mixture thus obtained is compressed using conventional tableting presses, equipped for obtaining tablets of the desired shape and dosage. The punches must be lubricated at the time of compression. Preferably, therefore, a tableting machine equipped with automatic distribution of a lubricant is used. The lubricant is preferably selected from sodium stearyl fumarate, stearic acid, magnesium stearate, talc, purified silica, kaolin. The amount of lubricant to use for lubricating the punches is preferably 0.2-3.0 wt.% relative to the total of the tableting mixture.

Preferably the enteric-coated pellets are mixed with the wet granulate of tableting excipients in the presence of a lubricant as well, which preferably is the same as is
used for lubricating the punches. Then the lubricant is preferably partly applied directly on the punches and partly mixed with the pellets and the tableting excipients. Preferably the mixture for tableting, on lubricated punches, has the following percentage composition by weight:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric pellets</td>
<td>20-40%</td>
</tr>
<tr>
<td>Wet granulate of excipients</td>
<td>60-80%</td>
</tr>
<tr>
<td>Lubricant</td>
<td>0-3%</td>
</tr>
</tbody>
</table>

More preferably the mixture comprises:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric pellets</td>
<td>25-35%</td>
</tr>
<tr>
<td>Wet granulate of excipients</td>
<td>65-75%</td>
</tr>
<tr>
<td>Lubricant</td>
<td>0.2-3%</td>
</tr>
</tbody>
</table>

For completeness and for better understanding of the invention, some examples of formulations according to the invention and preparation thereof are given below.

**Dosage:** 43.38 mg of esomeprazole magnesium dihydrate (equal to 40 mg of esomeprazole base) per tablet

**Example 1**

The neutrals are introduced into the fluidized bed with Wurster insert, and spraying of the suspension (prepared and maintained at 20°C) containing esomeprazole, polysorbate 80, povidone PEG and purified water in the following amounts, is begun:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole magnesium dihydrate</td>
<td>2800 g</td>
<td>20.32%</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>160 g</td>
<td>1.16%</td>
</tr>
<tr>
<td>Povidone</td>
<td>320 g</td>
<td>2.32%</td>
</tr>
<tr>
<td>PEG</td>
<td>20 g</td>
<td>0.14%</td>
</tr>
<tr>
<td>Purified water</td>
<td>10480 g</td>
<td>76.06%</td>
</tr>
<tr>
<td>Neutrals 60</td>
<td>1600 g</td>
<td></td>
</tr>
</tbody>
</table>
We found that the suspension described above, containing the active ingredient, must be maintained at a temperature not above 20°C, otherwise heating occurring during homogenization, produces gelation and the spraying operation becomes impossible.

After spraying all of the suspension described above, drying of the pellets is carried out in the same fluidized bed.

At the end of drying, the pellets thus obtained are forced through a vibrating screen equipped with a screen with holes 650 micron in diameter.

Next, these pellets are coated, still in the fluidized bed equipped with Wurster insert, with an aqueous solution based on mannitol in the following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (g)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>480</td>
<td>20%</td>
</tr>
<tr>
<td>Purified water</td>
<td>1920</td>
<td>80%</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>1N</td>
<td>sufficient to adjust the solution pH to 9-10</td>
</tr>
<tr>
<td>Pellets</td>
<td>4800</td>
<td></td>
</tr>
</tbody>
</table>

Operating conditions:
Air inlet temperature: 70°C
Air outlet temperature: 40-45°C
Temperature of cores: 40-45°C

Next, these pellets are additionally coated in a fluidized bed equipped with Wurster insert with an aqueous solution based on Eudragit L100-55 with the following composition:
Eudragit L 100-55 6114 g 19.86%
Glyceryl monostearate 105 g 0.34%
Triethyl citrate 1420 g 4.61%
Talc 276 g 0.90%
Paraffin 86.4 g 0.28%
Polysorbate 80 34.5 g 0.11%
Water 22757 g 73.9%
Pellets 5000 g

10 Operating conditions:
Air inlet temperature: 45°C
Air outlet temperature: 25-30°C
Temperature of cores: 25-30°C

15 Analysis of these enteric-coated pellets showed the following results:

Titre of esomeprazole magnesium dihydrate 204.9 mg/g
Release in the first 2 hours in HCl 0.1 0.5%
Release in the next 45 min at pH 6.8 10.1%

20 Example 2
A proportion of the pellets of example 1 is mixed with cellulose+mannitol (marketed by Avicel with the name HFE-102, it is a co-spray dried mixture with content of microcrystalline cellulose and mannitol of 83 wt.% and 17 wt.% respectively) in the following amounts:

Enteric-coated pellets 4234 g 30.25%
Cellulose+mannitol 9696 g 69.25%
Sodium stearyl fumarate 70 g 0.5%

With a tableting machine suitably set-up, tablets are formed at a dosage of 43.38 mg of esomeprazole magnesium dihydrate, having an average weight of 700 mg/tablet and hardness 11 kp obtained with compression force applied equal to 4.5 kN.
The aforementioned tablets have the following release profile:

Release in the first 2 hours in HCl 0.1 13.3%
Release in the next 45 min at pH 6.8 not carried out

5 Example 3
A proportion of cellulose+mannitol (Avicel HFE-102) is granulated in an automatic pan, soaking the powder with water acidified to pH 4 using hydrochloric acid, in the following amounts:

10 Cellulose+mannitol 10000 g
Water 250 g

When the test for weight loss on drying is performed on this compound, the result obtained is approx. 5%, since on cellulose+mannitol as it is, the test for weight loss on drying gives a result of approx. 2.6%.

At this point a proportion of the pellets of example 1 is mixed with cellulose+mannitol granules in the following amounts:

Enteric-coated pellets 4234 g 29.24%
Cellulose+mannitol granules at 5% w/w 10180 g 70.28%
Sodium stearyl fumarate 70 g 0.48%

With a tableting machine equipped with automatic distribution of the lubricant on the punches, tablets are formed at a dosage of 43.38 mg of esomeprazole magnesium dihydrate having an average weight of 724 mg/tablet and hardness 16 kp obtained with a compression force equal to 3.5 kN.

The aforementioned tablets are dried in an automatic pan.

These tablets have the following release figures:

Release in the first 2 hours in HCl 0.1 12.3%
Release in the next 45 min at pH 6.8 not carried out
Example 4
A proportion of cellulose+mannitol (Avicel HFE-1 02) is granulated in an automatic pan, soaking the powder with water acidified to pH 4 using hydrochloric acid, in the following amounts:

- Cellulose+mannitol: 10000 g
- Purified water: 800 g

When the test for weight loss on drying is performed on this compound, the result obtained is approx. 10%.

At this point a proportion of the pellets of example 1 is mixed with cellulose+mannitol granules in the following amounts:

- Enteric-coated pellets: 4234 g (28.28%)
- Cellulose+mannitol granules at 10% w/w: 10665 g (71.26%)
- Sodium stearyl fumarate: 70 g (0.46%)

With a tableting machine suitably set-up as described in example 3, tablets are formed at a dosage of 43.38 mg of esomeprazole magnesium dihydrate having an average weight of 748 mg/tablet and hardness 20 kp obtained by applying a compression force equal to 2.0 kN.

The aforementioned tablets are dried in an automatic pan.

These tablets have the following release profile:

- Release in the first 2 hours in HCl 0.1: 0.3%
- Release in the next 45 min at pH 6.8: 102.1%

Example 5
The tablets produced in example 4 are put in an automatic pan and coated with a colouring suspension with the following composition:
Operating conditions:
Air inlet temperature: 50°C
Air outlet temperature: 25-30°C
Temperature of cores: 25-30°C

Spray this suspension on the tablets until a weight increase of 25 mg/tablet is obtained. Once the predetermined average weight is reached, dry the tablets in an automatic pan.

These tablets have the following release figures:
Release in the first 2 hours in HCl 0.1  1.4%
Release in the next 45 min at pH 6.8  100.5%

Example 6
The neutrals are introduced into the fluidized bed with Wurster insert, and spraying of the suspension (prepared and maintained at 20°C) containing esomeprazole, polysorbate 80, povidone, PEG and purified water in the following amounts is begun:

Esomeprazole magnesium dihydrate 2800 g 20.32%
Polysorbate 80 160 g 1.16%
Povidone 320 g 2.32%
PEG 20 g 0.14%
Water 10480 g 76.06%
Neutrals 60 1600 g
Operating conditions:
Air inlet temperature: 90°C
Air outlet temperature: 40-50°C
Temperature of cores: 40-50°C

After spraying all the suspension described above, drying of the pellets is carried out in the same fluidized bed.
At the end of drying, the pellets thus obtained are forced through a vibrating screen equipped with a screen having holes with diameter of 650 micron.

Next, these pellets are coated, still in the fluidized bed equipped with Wurster insert, with an aqueous solution based on mannitol in the following amounts:

Mannitol 480 g 20%
Purified water 1920 g 80%
Sodium hydroxide 1N sufficient to adjust the solution pH to 9-10

Pellets 4800 g

Operating conditions:
Air inlet temperature: 70°C
Air outlet temperature: 40-45°C
Temperature of cores: 40-45°C

Next, these pellets are additionally coated in a fluidized bed equipped with Wurster insert with an aqueous solution based on Eudragit L100-55 with the following composition:

Eudragit L100-55 6114 g 19.86%
Glyceryl monostearate 105 g 0.34%
Triethyl citrate 1420 g 4.61%
Talc 276 g 0.90%
Paraffin 86.4 g 0.28%
Polysorbate 80 34.5 g 0.11%
Purified water 22757 g 73.90%
Pellets 5000 g

Operating conditions:
Air inlet temperature: 45 °C
Air outlet temperature: 25-30°C
Temperature of cores: 25-30 °C

Analysis of these enteric-coated pellets showed the following results:
Titre of esomeprazole magnesium dihydrate 202.1 mg/g
Release in the first 2 hours in HCl 0.1 0.3%
Release in the next 45 min at pH 6.8 102.7%

Example 7
A proportion of the pellets of example 6 is mixed with microcrystalline cellulose in the following amounts:

Enteric-coated pellets 4293 g 30.66%
Microcrystalline cellulose 9637 g 68.84%
Sodium stearyl fumarate 70 g 0.5%

With a tableting machine suitably set-up, tablets are formed at a dosage of 43.38 mg of esomeprazole magnesium dihydrate having an average weight of 700 mg/tablet and hardness 10 kp obtained with a compression force equal to 5.0 kN.

The aforementioned tablets have the following release profile:
Release in the first 2 hours in HCl 0.1 15.6%
Release in the next 45 min at pH 6.8 not carried out

Example 8
A proportion of the microcrystalline cellulose is granulated in an automatic pan, soaking the powder with water acidified to pH 4 using hydrochloric acid, in the following amounts:
Microcrystalline cellulose 10000 g
Purified water 150 g

On performing the test for weight loss on drying on this compound, the result obtained is approx. 5%, since on microcrystalline cellulose as it is, the test for weight loss on drying gives a result of approx. 3.4%.

At this point a proportion of the pellets of example 6 is mixed with microcrystalline cellulose granules in the following amounts:

Enteric-coated pellets 4293 g 29.64%
Microcrystalline cellulose granules at 5% w/w 10120 g 69.88%
Sodium stearyl fumarate 70 g 0.48%

With a suitable tableting machine equipped with automatic distribution of the lubricant on the punches, tablets are formed at a dosage of 43.38 mg of esomeprazole magnesium dihydrate having an average weight of 724 mg/tablet and hardness 14 kp obtained with a compression force equal to 3.5 kN.

The aforementioned tablets are dried in an automatic pan.

These tablets have the following release figures:

Release in the first 2 hours in HCl 0.1 14.6%
Release in the next 45 min at pH 6.8 not carried out

Example 9
A proportion of the microcrystalline cellulose is granulated in an automatic pan, soaking the powder with water acidified to pH 4 preferably using hydrochloric acid, in the following amounts:

Microcrystalline cellulose 10000 g
Purified water 650 g

On performing the test for weight loss on drying on this compound, the result obtained is approx. 10%.

At this point a proportion of the pellets of example 6 is mixed with microcrystalline cellulose granules in the following amounts:
Enteric-coated pellets 4293 g 28.69%
Microcrystalline cellulose granules at 10% w/w 10600 g 70.84%
Sodium stearyl fumarate 70 g 0.47%

With a tableting machine equipped with automatic distribution of the lubricant on the punches, tablets are formed at a dosage of 43.38 mg of esomeprazole magnesium dihydrate having an average weight of 748 mg/tablet and hardness 16 kp obtained with a compression force equal to 2.0 kN.

The aforementioned tablets are dried in an automatic pan. These tablets have the following release figures:
Release in the first 2 hours in HCl 0.1 2.4%
Release in the next 45 min at pH 6.8 96.1 %

Example 10
The tablets produced in example 9 are put in an automatic pan and coated with a colouring suspension with the following composition:
HPMC 5cps 202.3 g 5%
PEG 4000 26.3 g 0.65%
Talc 177.8 g 4.39%
Titanium dioxide 101.2 g 2.50%
Red iron oxide 5.14 g 0.13%
Yellow iron oxide 1.3 g 0.03%
Purified water 202.3 g 5%
Ethanol 3330 g 82.30%

Tablets 12000 g

Operating conditions:
Air inlet temperature: 50°C
Air outlet temperature: 25-30 °C
Temperature of cores: 25-30 °C
Spray this suspension on the tablets until a weight increase of 25 mg/tablet is obtained. Once the predetermined average weight is reached, dry the tablets in an automatic pan.

These tablets have the following release figures:

- Release in the first 2 hours in HCl 0.1 \( \text{mg/tablet} \) = 2.5%
- Release in the next 45 min at pH 6.8 \( \text{mg/tablet} \) = 98.4%

**Dosage:** 21.69 mg of esomeprazole magnesium dihydrate (equal to 20 mg of esomeprazole base) per tablet

**Example 11**

The neutrals are introduced into the fluidized bed with Wurster insert, and spraying of the suspension (prepared and maintained at 20 °C) containing esomeprazole, polysorbate 80, povidone, PEG and purified water in the following amounts is begun:

- Esomeprazole magnesium dihydrate 2800 g 20.32%
- Polysorbate 80 160 g 1.16%
- Povidone 320 g 2.32%
- PEG 20 g 0.14%
- Purified water 10480 g 76.06%
- Neutrals 60 1600 g

**Operating conditions:**

- Air inlet temperature: 90 °C
- Air outlet temperature: 40-50 °C
- Temperature of cores: 40-50 °C

After spraying all the suspension described above, drying of the pellets is carried out in the same fluidized bed.

At the end of drying, the pellets thus obtained are forced through a vibrating screen equipped with a screen having holes with diameter of 650 micron.
Next, these pellets are coated, still in the fluidized bed equipped with Wurster insert, with an aqueous solution based on mannitol in the following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>480 g</td>
<td>20%</td>
</tr>
<tr>
<td>Purified water</td>
<td>1920 g</td>
<td>80%</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>1N</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sufficient to adjust the solution pH to 9-10</td>
<td></td>
</tr>
</tbody>
</table>

Pellets 4800 g

10 Operating conditions:
- Air inlet temperature: 70°C
- Air outlet temperature: 40-45°C
- Temperature of cores: 40-45°C

Next, these pellets are additionally coated in a fluidized bed equipped with Wurster insert with an aqueous solution based on Eudragit L100-55 with the following composition:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit L100-55</td>
<td>6114 g</td>
<td>19.86%</td>
</tr>
<tr>
<td>Glyceryl monostearate</td>
<td>105 g</td>
<td>0.34%</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>1420 g</td>
<td>4.61%</td>
</tr>
<tr>
<td>Talc</td>
<td>276 g</td>
<td>0.90%</td>
</tr>
<tr>
<td>Paraffin</td>
<td>86.4 g</td>
<td>0.28%</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>34.5 g</td>
<td>0.11%</td>
</tr>
<tr>
<td>Water</td>
<td>22757 g</td>
<td>73.9%</td>
</tr>
</tbody>
</table>

Pellets 5000 g

Operating conditions:
- Air inlet temperature: 45°C
- Air outlet temperature: 25-30°C
- Temperature of cores: 25-30°C

Analysis of these enteric-coated pellets showed the following results:
Titre of esomeprazole magnesium dihydrate 199.6 mg/g
Release in the first 2 hours in HCl 0.1 0.2%
Release in the next 45 min at pH 6.8 99.8%

5 Example 12
A proportion of the pellets of example 11 is mixed with cellulose+mannitol (Avicel HFE-102) in the following amounts:

Enteric-coated pellets 4346 g 31.04%
Cellulose+mannitol 9584 g 68.46%
Sodium stearyl fumarate 70 g 0.5%

With a tableting machine suitably set-up, tablets are formed at a dosage of 21.69 mg of esomeprazole magnesium dihydrate having an average weight of 350 mg/tablet and hardness 7 kp obtained with a compression force equal to 5.0 kN.

The aforementioned tablets have the following release figures:
Release in the first 2 hours in HCl 0.1 11.6%
Release in the next 45 min at pH 6.8 not carried out

Example 13
A proportion of the cellulose+mannitol (Avicel HFE-102) is granulated in an automatic pan, soaking the powder with water acidified to pH 4 using hydrochloric acid, in the following amounts:

Cellulose+mannitol 10000 g
Water 250 g

On performing the test for weight loss on drying on this compound, the result obtained is approx. 5%, since on cellulose+mannitol as it is, the test for weight loss on drying gives a result of approx. 2.6%.

At this point a proportion of the pellets of example 11 is mixed with cellulose+mannitol granules in the following amounts:
Enteric-coated pellets 4346 g 30.02%
Cellulose+mannitol granules at 5% w/w 10062 g 69.50%
Sodium stearyl fumarate 70 g 0.48%

With a suitable tableting machine, tablets are formed at a dosage of 21.69 mg of esomeprazole magnesium dihydrate having an average weight of 362 mg/tablet and hardness 15 kp obtained with a compression force equal to 3.0 kN.
The aforementioned tablets are dried in an automatic pan.

These tablets have the following release figures:

10 Release in the first 2 hours in HCl 0.1 7.6%
Release in the next 45 min at pH 6.8 not carried out

Example 14

A proportion of the cellulose+mannitol (Avicel HFE-102) is granulated in an automatic pan, soaking the powder with water acidified to pH 4 using hydrochloric acid, in the following amounts:

Cellulose+mannitol 10000 g
Purified water 800 g

On performing the test for weight loss on drying on this compound, the result obtained is approx. 10%.
At this point a proportion of the pellets of example 11 is mixed with cellulose+mannitol granules in the following amounts:

Enteric-coated pellets 4346 g 29.05%
Cellulose+mannitol granules at 10% w/w 10542 g 70.48%
Sodium stearyl fumarate 70 g 0.47%

With a tableting machine equipped with automatic distribution of the lubricant on the punches, tablets are formed at a dosage of 43.38 mg of esomeprazole magnesium dihydrate having an average weight of 374 mg/tablet and hardness 25 kp obtained applying a compression force equal to 2.3 kN.
The aforementioned tablets are dried in an automatic pan.
These tablets have the following release figures:
Release in the first 2 hours in HCl 0.1 0.4%
Release in the next 45 min at pH 6.8 100.7%

5 Example 15
The tablets produced in example 14 are put in an automatic pan and coated with a colouring suspension with the following composition:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC 5cps</td>
<td>202.3 g</td>
<td>5%</td>
</tr>
<tr>
<td>PEG 4000</td>
<td>26.3 g</td>
<td>0.65%</td>
</tr>
<tr>
<td>Talc</td>
<td>177.8 g</td>
<td>4.39%</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>101.2 g</td>
<td>2.50%</td>
</tr>
<tr>
<td>Red iron oxide</td>
<td>51.4 g</td>
<td>0.13%</td>
</tr>
<tr>
<td>Yellow iron oxide</td>
<td>1.3 g</td>
<td>0.03%</td>
</tr>
<tr>
<td>Purified water</td>
<td>202.3 g</td>
<td>5%</td>
</tr>
<tr>
<td>Ethanol</td>
<td>3330 g</td>
<td>82.30%</td>
</tr>
<tr>
<td>Tablets</td>
<td>12000 g</td>
<td></td>
</tr>
</tbody>
</table>

20 Operating conditions:
Air inlet temperature: 50°C
Air outlet temperature: 25-30 °C
Temperature of cores: 25-30 °C

Spray this suspension on the tablets until a weight increase of 12.5 mg/tablet is obtained. Once the predetermined average weight is reached, dry the tablets in an automatic pan.

These tablets have the following release figures:
Release in the first 2 hours in HCl 0.1 0.6%
Release in the next 45 min at pH 6.8 100.1%

25 Example 16
The neutrals are introduced into the fluidized bed with Wurster insert, and spraying of the suspension (prepared and maintained at 20°C) containing esomeprazole, polysorbate 80, povidone, PEG and purified water in the following amounts is begun:
Esomeprazole magnesium dihydrate 2800 g 20.32%
Polysorbate 80 160 g 1.16%
Povidone 320 g 2.32%
PEG 5 20 g 0.14%
Water 10480 g 76.06%
Neutrals 60 1600 g

Operating conditions:
Air inlet temperature: 90°C
Air outlet temperature: 40-50 °C
Temperature of cores: 40-50 °C

After spraying all the suspension described above, drying of the pellets is carried out in the same fluidized bed.

At the end of drying, the pellets thus obtained are forced through a vibrating screen equipped with a screen having holes with diameter of 650 micron.

Next, these pellets are coated, still in the fluidized bed equipped with Wurster insert, with an aqueous solution based on mannitol in the following amounts:

Mannitol 480 g 20%
Purified water 1920 g 80%
Sodium hydroxide 1N sufficient to adjust the solution pH to 9.10

Pellets 4800 g

Operating conditions:
Air inlet temperature: 70°C
Air outlet temperature: 40-45 °C
Temperature of cores: 40-45 °C

Next, these pellets are additionally coated in a fluidized bed equipped with Wurster insert with an aqueous solution based on Eudragit L100-55 with the following composition:
Eudragit L100-55 6114 g 19.86%
Glyceryl monostearate 105 g 0.34%
Triethyl citrate 1420 g 4.61%
Talc 276 g 0.90%
Paraffin 86.4 g 0.28%
Polysorbate 80 34.5 g 0.11%
Purified water 22757 g 73.9%

Pellets 5000 g

Operating conditions:
Air inlet temperature: 45°C
Air outlet temperature: 25-30°C
Temperature of cores: 25-30°C

Analysis of these enteric-coated pellets showed the following results:
Titre of esomeprazole magnesium dihydrate 201.7 mg/g
Release in the first 2 hours in HCl 0.1 0.3%
Release in the next 45 min at pH 6.8 101.7%

Example 17
A proportion of the pellets of example 16 is mixed with microcrystalline cellulose in the following amounts:

Enteric-coated pellets 4301 g 30.72%
Microcrystalline cellulose 9629 g 68.78%
Sodium stearyl fumarate 70 g 0.5%

With a tableting machine suitably set-up, tablets are formed at a dosage of 21.69 mg of esomeprazole magnesium dihydrate having an average weight of 350 mg/tablet and hardness 5 kp obtained with a compression force equal to 5.0 kN.

The aforementioned tablets have the following release figures:
Release in the first 2 hours in HCl 0.1 12.6%
Release in the next 45 min at pH 6.8 not carried out

Example 18

5 A proportion of the microcrystalline cellulose is granulated in an automatic pan, soaking the powder with water acidified to pH 4 using hydrochloric acid, in the following amounts:

<table>
<thead>
<tr>
<th></th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline cellulose</td>
<td>10000 g</td>
</tr>
<tr>
<td>Purified water</td>
<td>150 g</td>
</tr>
</tbody>
</table>

On performing the test for weight loss on drying on this compound, the result obtained is approx. 5%, since on the microcrystalline cellulose as it is, the test for weight loss on drying gives a result of approx. 3.4%.

15 At this point a proportion of the pellets of example 16 is mixed with microcrystalline cellulose granules in the following amounts:

<table>
<thead>
<tr>
<th></th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric-coated pellets</td>
<td>4301 g 29.7%</td>
</tr>
<tr>
<td>Microcrystalline cellulose granules at 5% w/w</td>
<td>10110 g 69.82%</td>
</tr>
<tr>
<td>Sodium stearyl fumarate</td>
<td>70 g 0.48%</td>
</tr>
</tbody>
</table>

With a suitable tableting machine equipped with automatic distribution of the lubricant on the punches, tablets are formed at a dosage of 21.69 mg of esomeprazole magnesium dihydrate having an average weight of 362 mg/tablet and hardness 13 kp obtained with a compression force equal to 3.5 kN.

The aforementioned tablets are dried in an automatic pan.

These tablets have the following release figures:

<table>
<thead>
<tr>
<th></th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release in the first 2 hours in HCl 0.1</td>
<td>10.6%</td>
</tr>
<tr>
<td>Release in the next 45 min at pH 6.8</td>
<td>not carried out</td>
</tr>
</tbody>
</table>
Example 19
A proportion of the microcrystalline cellulose is granulated in an automatic pan, soaking the powder with water acidified to pH 4 using hydrochloric acid, in the following amounts:

Microcrystalline cellulose 10000 g
Purified water 650 g

On performing the test for weight loss on drying on this compound, the result obtained is approx. 10%.

At this point a proportion of the pellets of example 16 is mixed with microcrystalline cellulose granules in the following amounts:

Enteric-coated pellets 4301 g 28.74%
Cellulose+microcryst. granules at 10% w/w 10592 g 70.79%
Sodium stearyl fumarate 70 g 0.47%

With a tableting machine equipped with automatic distribution of the lubricant on the punches, tablets are formed at a dosage of 21.69 mg of esomeprazole magnesium dihydrate having an average weight of 748 mg/tablet and hardness 20 kp obtained with a compression force equal to 2.3 kN.

The aforementioned tablets are dried in an automatic pan.

These tablets have the following release figures:
Release in the first 2 hours in HCl 0.1 2.5%
Release in the next 45 min at pH 6.8 97.1%

Example 20
The tablets produced in example 19 are put in an automatic pan and coated with a colouring suspension with the following composition:

HPMC 5cps 202.3 g 5%
PEG 4000 26.3 g 0.65%
Talc 177.8 g 4.39%
Titanium dioxide 101.2 g 2.50%
Red iron oxide 5.1 4 g 0.1 3%
Yellow iron oxide 1-3 g 0.03%
Purified water 202.3 g 5%
Ethanol 3330 g 82.30%

Tablets 12000 g

Operating conditions:
Air inlet temperature: 50°C
Air outlet temperature: 25-30°C
Temperature of cores: 25-30°C

Spray this suspension on the tablets until a weight increase of 12.5 mg/tablet is obtained. Once the predetermined average weight is reached, dry the tablets in an automatic pan.

These tablets have the following release figures:
Release in the first 2 hours in HCl 0.1 2.6%
Release in the next 45 min at pH 6.8 97.9%
**43.38 mg of esomeprazole magnesium dihydrate**
*(equal to 40 mg of esomeprazole base)*

<table>
<thead>
<tr>
<th>Example 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active pellets per tablet</strong></td>
<td><strong>Cellulose + mannitol and SSF per tablet</strong></td>
</tr>
<tr>
<td>211.71 mg</td>
<td>488.29 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active pellets per tablet</strong></td>
<td><strong>Cellulose + mannitol/water and SSF per tablet</strong></td>
</tr>
<tr>
<td>211.71 mg</td>
<td>512.52 mg</td>
</tr>
</tbody>
</table>

<table>
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<th>Example 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active pellets per tablet</strong></td>
<td><strong>Cellulose + mannitol/water and SSF per tablet</strong></td>
</tr>
<tr>
<td>211.71 mg</td>
<td>536.77 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 7</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active pellets per tablet</strong></td>
<td><strong>Microcrystalline cellulose and SSF per tablet</strong></td>
</tr>
<tr>
<td>214.64 mg</td>
<td>485.36 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Example 8</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active pellets per tablet</strong></td>
<td><strong>Microcrystalline cellulose/water and SSF per tablet</strong></td>
</tr>
<tr>
<td>214.64 mg</td>
<td>509.45 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 9</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active pellets per tablet</strong></td>
<td><strong>Microcrystalline cellulose/water and SSF per tablet</strong></td>
</tr>
<tr>
<td>214.64 mg</td>
<td>533.54 mg</td>
</tr>
</tbody>
</table>

**Notes:**

5 SSF= sodium stearyl fumarate  
Cellulose+mannitol/water = cellulose + mannitol granulated with water  
Microcrystalline cellulose/water = microcrystalline cellulose granulated with water
### 21.69 mg of esomeprazole magnesium dihydrate
(equivalent to 20 mg of esomeprazole base)

<table>
<thead>
<tr>
<th>Example 12</th>
<th>Active pellets per tablet</th>
<th>Cellulose + mannitol and SSF per tablet</th>
<th>Compression force</th>
<th>Tablet hardness</th>
<th>Release in HCl 0.1</th>
<th>Release at pH 6.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>108.66 mg</td>
<td>241.34 mg</td>
<td>5.0 kN</td>
<td>7 kp</td>
<td>11.6%</td>
<td>/</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 13</th>
<th>Active pellets per tablet</th>
<th>Cellulose + mannitol/water and SSF per tablet</th>
<th>Compression force</th>
<th>Tablet hardness</th>
<th>Release in HCl 0.1</th>
<th>Release at pH 6.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>108.66 mg</td>
<td>253.31 mg</td>
<td>3.0 kN</td>
<td>15 kp</td>
<td>7.6%</td>
<td>/</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 14</th>
<th>Active pellets per tablet</th>
<th>Cellulose + mannitol/water and SSF per tablet</th>
<th>Compression force</th>
<th>Tablet hardness</th>
<th>Release in HCl 0.1</th>
<th>Release at pH 6.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>108.66 mg</td>
<td>265.30 mg</td>
<td>2.3 kN</td>
<td>25 kp</td>
<td>0.4%</td>
<td>100.7</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 17</th>
<th>Active pellets per tablet</th>
<th>Microcrystalline cellulose and SSF per tablet</th>
<th>Compression force</th>
<th>Tablet hardness</th>
<th>Release in HCl 0.1</th>
<th>Release at pH 6.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>107.53 mg</td>
<td>242.47 mg</td>
<td>5.0 kN</td>
<td>5 kp</td>
<td>12.6%</td>
<td>/</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 18</th>
<th>Active pellets per tablet</th>
<th>Microcrystalline cellulose/water and SSF per tablet</th>
<th>Compression force</th>
<th>Tablet hardness</th>
<th>Release in HCl 0.1</th>
<th>Release at pH 6.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>107.53 mg</td>
<td>254.50 mg</td>
<td>3.5 kN</td>
<td>13 kp</td>
<td>10.6%</td>
<td>/</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 19</th>
<th>Active pellets per tablet</th>
<th>Microcrystalline cellulose/water and SSF per tablet</th>
<th>Compression force</th>
<th>Tablet hardness</th>
<th>Release in HCl 0.1</th>
<th>Release at pH 6.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>107.53 mg</td>
<td>266.54 mg</td>
<td>2.3 kN</td>
<td>20 kp</td>
<td>2.5%</td>
<td>97.1</td>
<td></td>
</tr>
</tbody>
</table>

Notes:

5 SSF = sodium stearyl fumarate
Cellulose + mannitol/water = cellulose + mannitol granulated with water
Microcrystalline cellulose/water = microcrystalline cellulose granulated with water
Tablet hardness was assessed using the Erweka durometer model TBH 225 TD.

Discussion

It can be deduced from the examples that by compressing the enteric-coated pellets of esomeprazole with microcrystalline cellulose as it is (whether cellulose+mannitol or simple microcrystalline cellulose) the enteric-coated pellets are partially disintegrated during compression, damaging mainly the enteric coating.

It can also be seen from the examples that by compressing pellets of esomeprazole with cellulose granulated with water, the percentage of pellets that break during compression is reduced almost to zero when cellulose+mannitol soaked with water is used (with weight loss on drying equal to approx. 10%).

The foregoing applies to the tablets of both dosages.
A method for preparing MUPS tablets comprising esomeprazole, said method comprising the following steps:

(i) preparing enteric-coated microgranules (pellets) containing esomeprazole;

(ii) granulating tableting excipients with water in order to obtain a wet granulate whose water content is 6-15% by weight as regards said excipients; wherein said excipients include cellulose;

(iii) preparing a mixture comprising the enteric-coated microgranules obtained from step (i) and the wet granulate obtained from step (ii);

(iv) tableting the mixture obtained from step (iii) by a tableting force equal to 1.8-2.5 kN by lubricated punches.

2. Method according to claim 1 wherein said excipients further include an alditol having general formula H[CH(OH)]nH where n is ranging from 5 to 12.

3. Method according to claim 2 wherein said excipients are consisting of cellulose; or said excipients are consisting of a mixture of cellulose and an alditol having general formula H[CH(OH)]nH where n is ranging from 5 to 12.

4. Method according to any of the claims 1-3 wherein the mixture obtained from step (iii) exhibits the following percent composition by weight:
   - enteric-coated pellets 20-40%
   - excipient wet granulate 60-80%
   - lubricant 0.2-3%

5. Method according to any of the claims 1-4 wherein said microgranules comprise each:
   (a) an inert core;
   (b) a layer containing esomeprazole applied on said inert core;
   (c) an insulating layer consisting in mannitol, said insulating layer being applied on the layer (b);
   (d) an external coating consisting in an enteric-coated membrane; wherein said layer (b) containing esomeprazole contains no alkaline substance.

6. Method according to any of the claims 1-5 wherein after tableting the tablets undergo film casting.

7. Enteric-coated microgranules containing esomeprazole, said microgranules comprising each:
(a) an inert core;
(b) a layer containing esomeprazole applied on said inert core;
(c) an insulating layer consisting in mannitol, said insulating layer being applied on the layer (b);
(d) an external coating consisting in an enteric-coated membrane;

wherein said layer (b) containing esomeprazole contains no alkaline substance.

8. Pharmaceutical formulations of MUPS type comprising the microgranules according to claim 7.

9. MUPS tablets for oral administration of esomeprazole, said tablets achievable by the method according to any of the claims 1-6, said tablets having a hardness higher than 15 kp and having a delivery degree of esomeprazole in 0.1 M HCl in 2 hours lower than 3% by weight with respect to total esomeprazole contained therein.

10. MUPS tablets for oral administration of esomeprazole, said tablets including as tableting excipients cellulose or a mixture of cellulose and an alditol having general formula H[CH(OH)]nH where n is ranging from 5 to 12.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/20 A61K31/4439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal , BIOSIS, EMBASE, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>EP 1 452 172 A2 (ASTRAZENECA AB [SE]) 1 September 2004 (2004-09-01) examples 1-16 claim 1</td>
<td>1-10</td>
</tr>
<tr>
<td>Y</td>
<td>Wo 02/072071 AI (ASTRAZENECA AB [SE]; GLAD HAAKAN [SE]; SOEDERBOM MALIN [SE]) 19 September 2002 (2002-09-19) page 18, line 4 - line 15 examples 1-3</td>
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<tr>
<td>Y</td>
<td>Wo 2008/006534 A2 (LEK PHARMACEUTICALS [SI]; STANIC LJUBIN TIJANA [SI]; KOCEVAR KLEMEN [S]) 17 January 2008 (2008-01-17) page 13 - page 20</td>
<td>1-10</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another document, or to determine the existence of a prior art document but is no longer considered, in particular when the dates on which the means in question were made public by any of the means specified in paragraph I, or by the same inventor but in a different legal state.

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"P" document published prior to the international filing date but later than the priority date claimed

**I** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered as novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered as novel or cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"S" document member of the same patent family

Date of the actual completion of the international search 16 November 2011

Date of mailing of the international search report 24/11/2011

Name and mailing address of the ISA/Authorized officer

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Si ndel , Ul r i ke

Form PCT/ISA/210 (second sheet) (April 2005)
## DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>Y</td>
<td>wo 2010/041276 AI (JUBLANT ORGANOSYS LTD [IN]; RAJAN GOPAL [IN]; KUMAR PRATIK [IN]; MUKH) 15 April 2010 (2010-04-15) examples 1-7</td>
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<td>Patent document cited in search report</td>
<td>Publication date</td>
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<td>EP 1452172 A2</td>
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