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(54) **Title:** A FORMULATION COMPRISING BENZIMIDAZOLE

(57) **Abstract:** The present invention relates to pharmaceutical compositions comprising esomeprazole to be used in the treatment of diseases associated with gastric acid secretion disorder.

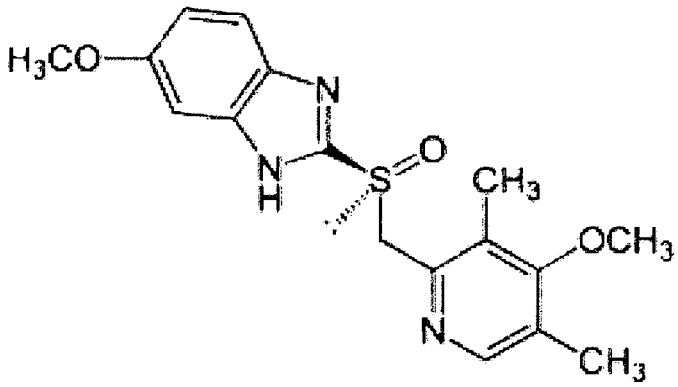
A FORMULATION COMPRISING BENZIMIDAZOLE

The present invention relates to use of calcium carbonate and dibasic sodium phosphate as buffer agent in pharmaceutical formulations comprising S enantiomer of omeprazole.

The present invention also relates to the ratio of the active agent to the buffer agents used in the formulation.

Omeprazole, which is a proton pump inhibitor, was firstly disclosed in the patent numbered EP 0005129. Certain salts of omeprazole, which inhibits gastric acid secretion, were disclosed in the patent numbered EP-124495. Enantiomers of omeprazole and certain salts thereof were disclosed in detail in the patent numbered WO 94/27988.

Esomeprazole [(S)-5-methoxy-2-[(4-methoxy-3.5-dimethylpyrridine-2-yl)methylsulfinyl]-3H-benzoimidazole] (Formula I) is S enantiomer of omeprazole, which is used in the treatment of peptic ulcer and gastroesophageal reflux diseases.



Formula (I)

Esomeprazole is an H^+, K^+ -ATPase enzyme inhibitor, which reduces gastric acid secretion with a specific mechanism of action. It is indicated in the treatment of gastroesophageal reflux disease (GERD); erosive reflux esophagitis; Zollinger - Ellison syndrome; long-term maintenance treatment of healed reflux esophagitis to prevent relapses and in the symptomatic treatment of gastroesophageal reflux disease. In the cases that oral treatment is not appropriate, parenteral treatment is administered. With an appropriate antibiotic combination, it is indicated in the treatment of duodenum ulcer associated with Helicobacter pylori and in the prevention of relapses in peptic ulcer associated with Helicobacter pylori in the Helicobacter pylori eradication. Esomeprazole is indicated in the treatment of gastric ulcers associated with the use of NSAIDs including COX-2 selective NSAIDs in the patients requiring constant NSAIDs (non-steroidal anti-inflammatory drugs) treatment; and in the prevention of gastric and duodenal ulcers associated with the use of NSAIDs including COX-2 selective NSAIDs in the patients under risk.

Esomeprazole is present as sodium and magnesium salts on the market. While sodium salt is present in the forms of 20 and 40 mg for intravenous administration, magnesium salt is present in 20 and 40 mg delayed-release capsules and 10, 20 and 40 mg oral solutions.

Esomeprazole is not stable in acidic medium like all the other 'pyrazoles' and easily degrades. It is relatively stable in alkali media. Esomeprazole magnesium salt is the most preferred form of esomeprazole. Its stability is affected by moisture, heat, organic solvents and, to some extent, by light. While the degradation half-life time of magnesium salt is 19 hours in a medium with a pH value of 6.8 at a temperature of 25 °C, the degradation half-life time decreases to 8 hours at 37°C. As a result, the degradation half-life of magnesium salt in a pH value of 6.8 depends on the temperature. This case particularly leads to degradation of the active agent during production and shortens shelf-life.

Besides, as omeprazole and its derivatives are not stable in acidic media, they should be protected from contacting with acidic gastric liquid and transmitted to the small intestine without degrading; and should be absorbed there.

In the prior art, various methods are used for substances from pyrazole group such as esomeprazole in order to enable them to remain stable in the formulation. These methods are generally like not using enteric-coatings with acidic structures or using inert interlayer. Because it was observed that entering-coatings with acidic structures interact with esomeprazole. Interaction of the active agent and the acidic enteric-coating is prevented by using one or more inert coatings in enteric-coated tablets or capsules.

The patent application numbered EPl 927354 mentions a formulation of a proton pump inhibitor and at least one buffer agent. However, instead of enteric-coating, one or more film-coating was used in this formulation.

The inventors have developed an esomeprazole formulation that can remain stable during shelf-life and is resistant to the production temperatures in the range of 25°C - 45°C. It was observed that the use of calcium carbonate and dibasic sodium phosphate as buffer agent in the esomeprazole formulation surprisingly affects the stability of the active agent in a positive way.

Within this scope, the invention relates to esomeprazole formulations comprising calcium carbonate and dibasic sodium phosphate.

In another aspect, the invention relates to a formulation with an Esomeprazole: $CaC0_3$: Na_2HP0_4 ratio in the range of 100:5:1 to 6:1.5:1, preferably in the range of 50:4.5:1 to 8:1.7:1, more preferably in the range of 25:3:1 to 20:2:1.

The formulation can optionally be in solid oral dosage forms comprising tablet; layered tablet (e.g. double layer tablet); capsule; enteric-coated or modified-release tablets; controlled-release tablet;

extended-release tablet; delayed-release tablet; slow- or fast-release tablet; fast soluble tablet; effervescent tablet; effervescent granule; fast soluble powder mixture; water-soluble powder, tablet or granule; granule; pellet; mini tablet; micro tablet; granule in capsule; pellet in capsule; mini tablet in capsule; micro tablet in capsule; dragee; orodispersible tablet; film tablet or a combination thereof. Said tablets and pellets can be enteric-coated, which is a preferred factor of the invention. The active agent is protected from gastric acid thanks to enteric-coating and the buffer agents increase the stability of the active agent as they have alkali structures.

Esomeprazole, used in the formulation, can be in the form of its pharmaceutically acceptable salts; though it is preferably magnesium salt. More preferably, it is in the form of esomeprazole magnesium trihydrate.

The formulation comprises calcium carbonate in the range of 1.5 to 5%. The formulation comprises dibasic sodium phosphate in the range of 0.025 to 1%. In the studies conducted, it was observed that the ratio of esomeprazole to these two buffer agents also affects the stability. The most stable formulations were obtained with a ratio of Esomeprazole: CaCC^: Na_2HP0_4 in the range of 100:5:1 to 6:1 .5:1.

Within this scope, in another aspect, the invention relates to a formulation with a ratio of Esomeprazole: $CaC0_3$: Na_2HP0_4 in the range of 100:5:1 to 6:1.5:1, preferably in the range of 50:4.5:1 to 8:1.7:1, more preferably in the range of 25:3:1 to 20:2:1.

The ratios were calculated on the basis of the total weight of the tablet.

Besides, the formulation comprises one or more diluent, lubricant, coating agent, surfactant, binder or filling agent.

The diluents that can be used in the formulation can be selected from a group comprising alkali metal carbonates such as calcium carbonate; alkali metal phosphates such as calcium phosphate; alkali metal sulphates such as calcium sulphate; cellulose derivatives such as cellulose, microcrystalline cellulose, cellulose acetate; magnesium oxide, dextrin, fructose, dextrose, glyceryl palmitostearate, lactitol, kaolinite, lactose, maltose, mannitol, simethicone, sorbitol, starch, pregelatinized starch, talc, xylitol and/or anhydrates, hydrates and/or pharmaceutically acceptable derivatives or combinations thereof.

The lubricants that can be used in the formulations can be selected from metallic stearates (such as magnesium stearate, calcium stearate, aluminium stearate), fatty acid esters (such as sodium stearyl fumarate), fatty acids (such as stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols (PEG), metallic lauryl sulphates (such as sodium lauryl sulphate, magnesium lauryl sulphate), sodium chloride, sodium benzoate, sodium acetate and talc.

The binders that can be used in the formulations can be selected from starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glycose, dextrose, lactose, maltodextrin; natural and synthetic gums; gelatin; cellulose derivatives such as microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose, methylcellulose, ethylcellulose; polyvinylpyrrolidone (povidone); polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as sorbitol, xylitol, mannitol; and water; or combinations thereof.

The filling agents that can be used in the formulations are used to carry the active agent and selected from a group comprising lactose, sugar, starch, modified starch, mannitol, sorbitol, inorganic salts, microcrystalline cellulose, cellulose, calcium sulphate, xylitol and lactitol.

The surfactants that can be comprised in the formulations can be selected from polyoxyethylene-sorbitan-fatty acid esters (polysorbates), sodium lauryl sulphate, sodium stearyl fumarate, polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyethylene glycols (PEG), polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, aminoacids such as L-leucine, sugar esters of fatty acids and glycerides of fatty acids.

The enteric-coating agents in the formulation can be selected from cellulose derivatives such as hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, carboxymethyl ethyl cellulose, cellulose acetate phthalate; acrylic acid derivatives such as methacrylic acid copolymer L, methacrylic acid copolymer LD and methacrylic acid copolymer S; and natural substances such as shellac; or combinations thereof.

Conventionally well-known coating agents are methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, cellulose acetate phthalate, ethylcellulose, polyvinylpyrrolidone, sodium ethylcellulose sulphate and polyvinylacetatephthalate, hypromellose, shellac and hydroxyalkyl cellulose.

The formulation of the invention can be produced by any tablet or pellet production method in the prior art. The methods of tablet production in the prior art are wet granulation, dry granulation or direct compression method. The steps in the following example can be applied for wet granulation method:

=> The active agent mixture is obtained by mixing the active agent and the excipients.

⇒ A granulation solution is prepared by mixing the binder, solvent and the surfactant.

=> The active agent mixture is granulated with the granulation solution.

=> The obtained granules are dried and sieved.

=> Then, they are treated with the lubricant and compressed into tablets under appropriate conditions.

⇒ The tablets are coated with film-coating or enteric-coating.

The temperature applied through the production process should be in the range of 25-45 °C.

The following method can be applied for dry granulation:

=> The active agent and the other excipients apart from the lubricant/lubricants are mixed.

=> Then, the mixture is treated with the lubricant/lubricants and compressed into tablets.

=> The compressed tablets are coated with film-coating or enteric-coating.

The following steps can be applied for direct compression method:

=> The active agent mixture is prepared by mixing the active agent and the excipients.

⇒ The mixture is compressed into tablets under appropriate pressure and conditions.

=> The compressed tablets are coated with film-coating or enteric-coating.

Pellet production method is as follows:

=> The active agent mixture is prepared by mixing the active agent and the excipients.

=> A granulation solution is prepared by mixing the binder, solvent and the surfactant.

=> The pellets are obtained by coating the filling agent with the granulation solution and the active agent mixture obtained in the first step.

=> The obtained pellets are dried and coated with film-coating or enteric coating.

While the formulation is produced by one of these methods, calcium carbonate and dibasic sodium phosphate should be added into the formulation in the same phase.

The formulation is preferably granulated by wet granulation method and the tablets obtained through compressing pellets or granules obtained from granulation are coated with enteric-coating.

Preferably, the production by wet granulation is carried out at a temperature in the range of 25°C to 45°C.

EXAMPLES

EXAMPLE 1: Pellet form comprising esomeprazole

Content	% amount in unit dose
Active Agent	
Esomeprazole	22.5
Excipients	
Calcium carbonate	2.5
Dibasic sodium phosphate	1.0
Diluent	35.0
Sub-coating agent	7.4
Enteric-coating agent	16.0
Surfactant	0.1
Lubricant	4.4
Coloring agent	1.1
Filling agent	10.0
Total	**100.0**

Esomeprazole, diluent, dibasic sodium phosphate and calcium carbonate are mixed and the filling agent is coated with this dry mixture. The prepared pellets are granulated by wet granulation method. And then they are coated with the sub-coating agent and the enteric-coating agent. These are formed into a pharmaceutical composition by the conventional methods in the prior art.

EXAMPLE 2: Tablet dosage form comprising esomeprazole

Content	% amount in unit dose
Active Agent	
Esomeprazole	7.0
Excipients	
Calcium carbonate	1.6
Dibasic sodium phosphate	0.5
Diluent	50.0
Coating agent	11.0
Surfactant	0.1
Lubricant	3.4
Coloring agent	0.1
Filling agent	26.3
Total	**100.0**

Esomeprazole, diluent, the filling agent, dibasic sodium phosphate and calcium carbonate are mixed; the prepared mixture is granulated by wet granulation method. After the obtained mixture is treated with the lubricant; tablets are prepared by tablet compression method. Then, the tablets are coated with sub-coat and enteric-coating. These are formed into a pharmaceutical composition by the conventional methods in the prior art.

The pharmaceutical formulations of the invention comprising the active agent esomeprazole, which is a proton pump inhibitor, is indicated in the treatment of gastroesophageal reflux disease (GERD); erosive reflux esophagitis; long-term maintenance treatment of healed reflux esophagitis to prevent relapses; and in the symptomatic treatment of gastroesophageal reflux disease. In the cases that oral treatment is not appropriate, parenteral treatment is administered. With an appropriate antibiotic combination, it is indicated in the treatment of duodenum ulcer associated with Helicobacter pylori and in the prevention of relapses in peptic ulcer associated with Helicobacter pylori in the Helicobacter pylori eradication. Esomeprazole is indicated in the treatment of gastric ulcers associated

with the use of NSAIDs including **COX-2** selective NSAIDs in the patients requiring constant NSAIDs (non-steroidal anti-inflammatory drugs) treatment; and in the prevention of gastric and duodenal ulcers associated with the use of NSAIDs including **COX-2** selective NSAIDs in the patients under risk. Besides, esomeprazole is used in the treatment of gastro-intestinal ulcer and duodenum ulcer caused by Chorn disease.

CLAIMS

1. A pharmaceutical formulation comprising esomeprazole to be used in diseases associated with gastric acid secretion disorder, characterized in that said formulation comprises dibasic sodium phosphate and calcium carbonate.

2. The pharmaceutical formulation according to claim 1, characterized in that esomeprazole in the formulation is magnesium salt of esomeprazole.

3. The pharmaceutical formulation according to claim 2, characterized in that esomeprazole in the formulation is in the form of magnesium salt trihydrate.

4. The pharmaceutical formulation according to claim 1, characterized in that the ratio of dibasic sodium phosphate in the formulation is in the range of 0.025 to 1.

5. The pharmaceutical formulation according to claim 1, characterized in that the ratio of calcium carbonate in the formulation is in the range of 1.5 to 5.

6. The pharmaceutical formulation according to claim 1, characterized in that the ratio of esomeprazole: dibasic sodium phosphate: calcium carbonate in the formulation is in the range of 100:5:1 to 6:1.5:1.

7. The formulation according to any one of the preceding claims, wherein said formulation optionally comprises other pharmaceutically acceptable excipients.

8. A method for the production of a formulation in accordance with any one of the preceding claims, characterized in that esomeprazole, dibasic sodium phosphate and calcium carbonate are formulated together.

9. The pharmaceutical formulation according to claim 8, characterized in that esomeprazole, dibasic sodium phosphate, calcium carbonate and other excipients are granulated by wet granulation method.

10. The pharmaceutical formulation according to claim 8, characterized in that the temperature in production process is in the range of 25 to 45 °C.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/0OQ201

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61 K47/02 A61K9/28 A61 K9/50 A61K3 1/4439
ADD.

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 practicable, search terms used)

EPO-Internal , BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/ 134611 Al (HETERO DRUGS LTD [IN]; SRINIVAS REDDY MALE [IN]; VENKATESWAR REDDY POT) 21 December 2006 (2006-12-21) claims 183-185 example 13	1-10
X	W0 2011/083402 A2 (M0HAMED SHAFEE MUNEERA [SA]; KANDASAMY RUCKMANI [IN]; OMAR ABDULGANI T) 14 July 2011 (2011-07-14) claims 1,8,10,12	1-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2012/0OQ201

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006134611 A1	21-12-2006	NONE	
WO 2011083402 A2	14-07-2011	EP 2523654 A2	21-11-2012
		US 2011171295 A1	14-07-2011
		W0 2011083402 A2	14-07-2011