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(54) Title: PROCESS FOR THE PREPARATION OF OPTICALLY PURE OMEPRAZOLE

(57) Abstract: The present invention relates to a process for the preparation of substantially optically pure omeprazole, or a pharmaceutically acceptable salt or solvate thereof. The invention also relates to a process for preparing a pharmaceutical composition comprising the substantially optically pure omeprazole or the pharmaceutically acceptable salt or solvate thereof and to intermediates useful for the preparation of optically pure omeprazole.



WO 2008/092939 A2

Process for the preparation of optically pure omeprazole

The present invention relates to a process for the preparation of optically pure or optically enriched omeprazole and the
5 pharmaceutically acceptable salts and solvates thereof by optical resolution. The invention also provides intermediates useful for the preparation of optically pure omeprazole.

Background of the invention

10 Omeprazole is the common name for 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole. Omeprazole was first described in EP-A-0 005 129 and is well known as an effective gastric acid secretion inhibitor.

15 The sulfur atom of omeprazole is chiral. Thus, omeprazole exists in two enantiomeric forms, i.e. the (R)-enantiomer and the (S)-enantiomer, otherwise known as (R)-omeprazole and (S)-

- 2 -

omeprazole, respectively. (S)-Omeprazole is also referred to as esomeprazole.

Using non-stereoselective synthesis, omeprazole is obtained as a racemic mixture. Due to differences in pharmacokinetic properties of the (R)- and (S)-isomers of omeprazole, there is a general demand for methods allowing for the preparation of optically pure omeprazole.

Methods for the separation of the enantiomers of omeprazole are known in the art.

DE-A-40 35 455 (BYK GULDEN LOMBERG CHEM. FAB.) relates to a resolution process for obtaining optically pure omeprazole via formation of diastereomeric ethers.

WO-A-94/27988 discloses optical resolution of omeprazole using esters of omeprazole with chiral organic acids such as (R)-mandelic acid.

WO-A-96/02535 discloses a process for the preparation of the single enantiomers of omeprazole by asymmetric oxidation of the corresponding "prochiral" sulfide. The process employs an oxidizing agent in the presence of a chiral titanium complex.

Optical resolution of omeprazole by bioreduction is described in WO-A-96/17077, and an enantioselective preparation of omeprazole by biooxidation is described in WO-A-96/17076.

WO-A-97/02261 discloses a process for the optical purification of certain enantiomerically enriched benzimidazole derivatives using a crystallization method.

WO-A-02/098423 relates to an inclusion complex of (S)-omeprazole with cyclodextrin.

- 3 -

CN-A-1223262 relates to a process for the preparation of certain optically pure benzimidazole derivatives by inclusion complexation with binaphthyl phenol derivatives.

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WO-A-2007/074099 relates to an analogous process using (S)-1,1,2-triphenyl-1,2-ethanediol.

10

Cinchona alkaloids have found a number of applications as resolving agents for the fractionated crystallization of chiral acids as diastereomeric salts [P. Newman, Optical Resolution Procedures for Chemical Compounds, Volume 2, Part I and II, Optical Resolution Information Center, Manhattan College, Riverdale, N.Y. 10471, 1981]. For example, the racemic pantho-
15 tenic acid has been resolved by means of quinine or cinchonidine methohydroxide as described in J. Amer. Chem. Soc. 1941, 63, 1237. Resolution of racemic substituted γ -butyrolactone with cinchona methohydroxide is described in J. Amer. Chem. Soc. 1941, 63, 1368.

20

IPCOM000126473D discloses an optical resolution process wherein the diastereomeric pair of omeprazole N-benzyl cinchoninium salts is prepared by reactions under non-homogeneous conditions or under conditions employing a large excess of
25 omeprazole. These procedures have not been found practical and economical on an industrial scale.

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Thus, there remains a need for an improved process for preparing substantially optically pure omeprazole that does not suffer from the disadvantages of the known methods.

- 4 -

Description of the invention

It is an object of the present invention to provide a process for preparing substantially optically pure omeprazole which
5 process can advantageously be applied on an industrial scale.

It has surprisingly been found that this object can be achieved by a process according to the different aspects and embodiments of the present invention.

10

I. Optical resolution

In one aspect, the invention relates to a process for the preparation of substantially optically pure or enantiomeri-
15 cally enriched omeprazole by optical resolution.

General embodiment 1

20 In one general embodiment, the invention relates to a process for the preparation of enantiomerically enriched omeprazole by resolution of omeprazole with a resolving agent, more particularly with different resolving agents selected from chiral amines which form with omeprazole chemical interaction and
25 could be treated as diastereomeric salts.

An "enantiomerically enriched omeprazole" in the context of this general embodiment means a form of omeprazole which contains more than 50 % of one of the enantiomers, preferably
30 more than 65 %, even more preferably more than 80% of (R)- or (S)-enantiomer of omeprazole.

Examples of resolving agents include (+)-quinidine, (-)-strychnine, (-)-ephedrine, (-)-brucine, (-)-quinine, (-)-
35 cinchonidine, (+)-hydroquinidine, ((-) or (+))- α -methylben-

- 5 -

methybenzylamine, (-)-benzyl- α -methybenzylamine, (-)-2-amino-butanol, (+)-2-amino-1-phenyl-1,3-propanediol, ((-) or (+))-phenylalaninol, (+)-prolinol, ((+) or (-))-1-phenyl-propylamine, (+)-cinchonine, (+)-benzyl- α -methybenzyl-amine, (+)-dehydro-abietyl amine, (-)-2-amino-1-phenyl-1,3-propanediol, (-)-nicotine, (-)-pseudoephedrine, (+)-methy-ephedrine.

More particularly, this general embodiment relates to a process for the preparation of enantiomerically enriched omeprazole by resolution of omeprazole with a resolving agent selected from (+)-quinidine, (-)-brucine, (-)-cinchonidine and (+)- α -methybenzylamine.

A preferred process according to this general embodiment of the invention comprises:

- a) contacting the racemic omeprazole with resolving agent in a suitable solvent to prepare a clear solution,
- b) precipitating the diastereomeric salt,
- c) separating the precipitated diastereomeric salt and optionally isolating the diastereomeric salt remained in the solution,
- d) repeating the crystallization of diastereomeric salt if necessary,
- e) converting diastereomeric salt into enantiomerically enriched omeprazole.

The resolution can be performed in any suitable organic or inorganic solvent. Preferably, the solvent used for resolution is selected from water, hydrocarbon, halogenated hydrocarbon, ether, ester, ketone, nitrile and alcohol or a mixture thereof. More preferably, the solvent used for resolution is selected from methanol, ethanol, propanol, isopropanol and isobutanol.

- 6 -

Enantiomerically enriched omeprazole can be isolated from precipitated diastereomeric salt by dissolving the diastereomeric salt in acidic solution and further extraction with suitable organic solvent. In the case of isolation of enantiomerically enriched omeprazole from remaining diastereomeric salt solution, the solution is acidified and extracted with any suitable organic solvent. Preferably, the organic solvent for extraction is selected from hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, nitriles or alcohol or a mixture thereof. Most preferably, the solvent for extraction is ethyl acetate.

Diastereomeric salts have different physical properties and one can apply several methods to separate such salts. The methods can apply for instance difference in solubility, difference in adsorption, difference in partitioning coefficient and so on. Crystallizations, liquid/liquid and liquid/solid extractions, and several chromatographic principles for purification could be applied for separation of diastereomeric salt of omeprazole.

The enantiomerically enriched omeprazole can be further purified with the chromatographic methods disclosed according to general embodiment 3 below or with the chromatographic methods disclosed in prior art such as WO-A-2003/051867. Pure (R)- or (S)-omeprazole prepared according to this general embodiment can be further used in the preparation of pharmaceutically acceptable salts such as magnesium esomeprazole.

Preferred embodiment of general embodiment 1

According to a preferred embodiment of general embodiment 1, the invention relates to a process for the preparation of sub-

- 7 -

stantially optically pure omeprazole, or a pharmaceutically acceptable salt or solvate thereof, comprising the steps of:

- 5 (a) contacting omeprazole or a salt thereof with a resolving agent selected from a chiral amine or a chiral quaternary ammonium salt in a solvent to give a diastereomeric pair of omeprazole ammonium salts;
- 10 (b) separating the diastereomeric pair of omeprazole ammonium salts to give a substantially optically pure omeprazole ammonium salt;
- 15 (c) converting the substantially optically pure omeprazole ammonium salt to obtain substantially optically pure omeprazole or a pharmaceutically acceptable salt or solvate thereof; and
- 20 (d) optionally transforming the substantially optically pure omeprazole into a pharmaceutically acceptable salt or solvate thereof.

The process according to this preferred embodiment of the invention offers several advantages. It proceeds with high yield and high enantiomeric purity > 90% e.e. Furthermore, the resolving agents can be readily recovered after optical resolution. The process is easily industrialisable using tailored chiral amines or chiral quaternary ammonium salts and can be carried out under very mild, homogenous conditions. Moreover, the process does not require toxic solvents and can be applied without chromatographic separations.

A "substantially optically pure" isomer in the context of this preferred embodiment of the invention means an isomer with a diastereomeric excess (d.e.) or enantiomeric excess (e.e.) acceptable for a chiral compound prepared on industrial scale.

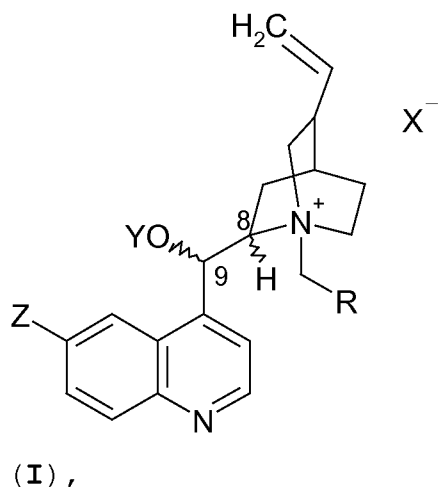
- 8 -

Such d.e. and e.e. values are readily determined by a person skilled in the art. Usually, a process is suitable for preparation on industrial scale with an d.e. or e.e. of at least 85 %, preferably of at least 90 % and more preferably of at least 95 %.

Omeprazole used according to this preferred embodiment of the invention can be prepared by any known methods, for example such as those disclosed in EP-A-5129, EP-A-103 553, EP-A-302 720, EP-A-369 208, EP-A-533 752, EP-A-533 264 and EP-A-484 265. The crystal form of omeprazole can be A, B or C according to WO-A-99/08500; Ohishi et al., Acta Cryst. 1989, C45, 1921-1923; and WO-A-2002/085889 respectively. Purity of starting omeprazole is preferably greater than 95 %, more preferably greater than 98 %.

Preferably, the resolving agent is selected from the group consisting of (-)-brucine, (+)- α -methylbenzylamine, (-)-ephedrine, N,N-dimethylephedrine, bis-(1-phenylethyl)amine, cinchona bases, derivatives thereof and quaternary salts thereof.

It is further preferred that the resolving agent is a quaternary cinchona salt of formula (I):



- 9 -

wherein

Z is hydrogen or methoxy;

5 Y is hydrogen, benzyl or allyl;

R is hydrogen or phenyl;

X is iodine, bromine, chlorine or hydroxy;

10 and wherein the configuration at C(8) and C(9) is independently (R) or (S).

Quaternary salts of cinchona alkaloids as resolving agents are inexpensive, commercially available or can easily be prepared in both enantiomeric forms, and are also non-toxic and recoverable. It is particularly preferred that the resolving agent is a quaternary salt of a cinchona base selected from the group consisting of (-)-quinine, (+)-quinidine, (+)-cinchonine and (-)-cinchonidine.

20 According to the process of this preferred embodiment of the invention, racemic or optionally enantiomerically enriched omeprazole or a salt thereof is contacted with a resolving agent as defined above in a suitable solvent. The contacting may be carried out in a conventional manner such as under stirring at ambient temperature.

In a preferred embodiment of step (a), the solvent of step (a) comprises at least one solvent which is selected from the group consisting of (C₁-C₅) alcohols, (C₃-C₆) ketones, acetonitrile, dimethylformamide, aromatic (C₆-C₉) hydrocarbons, tetrahydrofuran, aliphatic (C₁-C₄) esters, halogenated aliphatic (C₁-C₉) hydrocarbons and optionally comprises up to 50 vol-% water. More preferably, said solvent is selected from the group consisting of methanol, ethanol, acetone, butanone, dimethylformamide, tetrahydrofuran, dichloromethane, and aceto-

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nitrile. It is particularly preferred that the solvent comprises no more than 35 vol-%, preferably no more than 20 vol-%, most preferably no more than 15 vol-% water.

5 The resolving agent may generally be applied in any suitable molar amount. Preferably, the resolving agent is used in an amount of at least 0.7 equivalents, particularly at least 0.9 equivalents, most preferably at least 1 equivalent, based on the molar amount of omeprazole.

10

It is possible to recover the diastereomeric pair of omeprazole ammonium salts between steps (a) and (b) and such optional recovery may generally be carried out using conventional measures such as filtration and/or removal of solvent under reduced pressure. Preferably, this recovery comprises evaporation of solvent(s) under reduced pressure.

15 In one embodiment of step (b), separation of the diastereomeric pair of omeprazole ammonium salts comprises crystallizing omeprazole ammonium salt from a suitable solvent for crystallization. Preferably, the solvent for crystallization comprises at least one solvent selected from the group consisting of (C₁-C₅) alcohols, (C₃-C₆) ketones, acetonitrile, dimethylformamide, aromatic (C₆-C₉) hydrocarbons, tetrahydrofuran, aliphatic (C₁-C₄) esters, halogenated aliphatic (C₁-C₉) hydrocarbons. Particularly, the solvent for crystallization of step (b) may be the same or different from the solvent of step (a).

20 In a further preferred embodiment of step (b), step (b) is repeated at least once, such as once, twice, three times, etc. Thus, the omeprazole ammonium salt is recrystallized, thereby resulting in a considerable rise in d.e. reproducibly giving omeprazole ammonium salt of > 90 % d.e. Thus, omeprazole ammonium salt obtained from a first crystallization is typically subjected to recrystallization. Recrystallization can be ef-

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- 11 -

fectected in the same solvent system as defined above and can be carried out at a temperature in the range of from ambient temperature to the reflux temperature of the solvent. Finally the batch is usually filtered and washed with solvent.

5

Crystallization and recrystallization of omeprazole ammonium salt from a suitable solvent system may be carried out in a conventional manner. Diastereomeric salt resolution proved to be a dynamic process with the diastereomeric excess (d.e.) of the crystals enriching over time. Typically, a sample of the solids is isolated from the crystallization mixture for d.e. determination (e.g. d.e. criterion >90% d.e.).

In a preferred embodiment of step (c), converting the omeprazole ammonium salt comprises contacting the omeprazole ammonium salt with at least one compound selected from the group consisting of an acid, e.g. hydrochloric acid, an acidic salt, e.g. MgCl_2 or NH_4Cl , and an acidic ion exchanger, e.g. Dowex 50W H^+ .

20

Preferably, the conversion of step (c) is carried out in a suitable solvent system comprising water and at least one water-immiscible solvent. More preferably, the water-immiscible solvent is selected from the group consisting of aromatic ($\text{C}_6\text{-C}_9$) hydrocarbons, aliphatic ($\text{C}_2\text{-C}_8$) ethers, aliphatic ($\text{C}_1\text{-C}_4$) esters, halogenated aromatic or aliphatic ($\text{C}_1\text{-C}_9$) hydrocarbons, and mixtures thereof. Particularly preferred are toluene, dichloromethane, ethyl or butyl acetate and *tert*-butyl methyl ether. When the conversion step is carried out in the presence of a water-immiscible solvent, further steps of washing and removal of the solvent may be required.

Enantiomerically enriched esomeprazole can be further optically purified by preparative chromatography, such as HPLC or SMB chromatography. For example, methods generally disclosed

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- 12 -

in WO-A-2003/051867, CN-A-1683368 or WO-A-2007/071753 can be used.

Alternatively, without prior neutralization an alkaline or alkaline earth metal salt of omeprazole can be isolated directly in a substantially optically pure form from the aqueous phase by conventional methods. The alkaline metal cation can be replaced by another metal cation prior to isolation by treatment with an appropriate alkaline earth metal salt such as an alkaline earth halide such as magnesium chloride as described for example in WO-A-94/27988.

Furthermore, neutral optically pure omeprazole can optionally be subsequently transformed into a pharmaceutically acceptable optically pure omeprazole salt with an appropriate base by conventional methods, in particular into an alkaline, alkaline earth or transitional metal salt such as a lithium, sodium, potassium, magnesium, calcium, barium or zinc salt. Sodium and magnesium salts are particularly preferred. Other non-metal salts such as amine salts can also be prepared. Above mentioned pharmaceutically acceptable salts and methods for their preparation are generally disclosed in WO-A-94/27988, EP-A-984 957, EP-A-1 375 497, WO-A-2004/020436, WO-A-2004/037253, WO-A-2004/046134, WO-A-2004/089935, EP-A-1 273 581, EP-A-1 149 090, WO-A-2004/111029, WO-A-2006/001753, WO-A-2006/1755, WO-A-2004/099182, CN-A-1683369, WO-A-2006/073779, WO-A-2004/099181, WO-A-2003/074514, WO-A-2005/023796, WO-A-2005/23797, DE-A-10 2005 008412, EP-A-1 726 305 and RD462058.

It is particularly preferred that the pharmaceutically acceptable solvate is (S)-omeprazole magnesium dihydrate form A. Starting from (S)-omeprazole magnesium prepared according to the process described above, (S)-omeprazole magnesium dihydrate form A can be obtained according to the method disclosed in example 6 of WO-A-98/54171.

- 13 -

According to the process of this preferred embodiment of the present invention, selective formation of either one of the two diastereomeric ammonium salts can be advantageously controlled by using a suitable chiral quaternary ammonium salt. By way of example, using a cinchoninium salt as resolving agent will result in crystallization of the (S)-compound whereas using a cinchonidinium salt as resolving agent will result in crystallization of the (R)-compound. Thus, the process can be controlled such that crystals of the (S)-compound are obtained from fractionated crystallization, and crystals of the (R)-compounds may subsequently be isolated from the mother liquor. Alternatively, the process can be controlled such that crystals of the (R)-compound are obtained from fractionated crystallization and crystals of the (S)-compound may subsequently be isolated from the mother liquor.

According to one particularly preferred embodiment, racemic compound is dissolved in ethanol, acetone, dimethylformamide, dichloromethane, tetrahydrofuran or the like organic solvent. The reaction is not sensitive to water, thus a limited amount of water may be there such as up to 50 vol-%. N-benzylcinchonine hydroxide solution in an aforementioned solvent is added thereto in an equivalent molar amount, and then the mixture is concentrated in vacuo to obtain N-benzyl cinchoninium salt of the corresponding compound as a solid material. The isolated substance is dissolved in ethanol, isopropanol, butanol, methyl ethyl ketone, ethyl acetate or mixtures thereof, and the solution is left to stand to form crystals. The crystals are recovered by filtration of the solution and subjected to recrystallization to obtain the N-benzylcinchoninium salt of (S)-compound. The salt is treated with hydrochloric acid and recrystallized from an organic solvent in a conventional manner to obtain the desired (S)-compound. After the (S)-compound is filtered off, the mother

- 14 -

liquor may be concentrated by evaporation of solvent to obtain N-benzyl cinchoninium salt of the compound mainly containing the (R)-compound and which may subsequently be treated with hydrochloric acid to obtain crystals of the compounds containing mainly the (R)-compound.

According to another particularly preferred embodiment, an alkali metal salt of the racemic starting compound is dissolved in methanol, dimethylformamide, acetonitrile, tetrahydrofuran or the like organic solvent and/or water, and N-methyl cinchonidine iodide in an aforementioned organic solvent is added thereto in an equivalent molar amount. Water-immiscible solvents also may be occasionally used. The organic solvent is then concentrated in vacuo to obtain the N-methyl cinchonidine salt of the corresponding compound as a solid material. The diastereomeric pair of salts is dissolved in ethanol, isopropanol, butanol, methyl ethyl ketone, ethyl acetate or the like organic solvent and left to stand to obtain crystals which are recrystallized to obtain N-methylcinchonidinium salt of the (R)-compound. After the (R)-compound is filtered off, the mother liquor may be concentrated by evaporation of solvent to obtain N-methylcinchonidinium salts of the compounds mainly containing the (S)-compound. The (S)-salt is acidified with hydrochloric acid and recrystallized from an organic solvent to obtain the desired (S)-compound. Alternatively the desired (S)-compound is liberated straightforward from the mother liquor by addition of acid.

The invention also relates to a process for preparing a pharmaceutical composition comprising substantially optically pure omeprazole, or a pharmaceutically acceptable salt or solvate thereof, in combination with at least one pharmaceutically acceptable carrier, which includes the step of preparing the substantially optically pure omeprazole or the pharmaceutically acceptable salt or solvate thereof according to the pro-

- 15 -

cess of the invention. Preferably, the solvate is (S)-omeprazole magnesium dihydrate form A.

5 The particle size of the (S)-omeprazole and pharmaceutically acceptable salts or solvates used in the processes of the present invention is preferably in the range of 0.1-250 microns. If smaller particles are needed, they can be milled or micronized optionally together with other excipients. During this process the mechanical force on the particle surface
10 leads to a particle size reduction. For this purpose an air jet mill, a ball mill or a hammer mill are commonly used as milling equipment. The basic principle of the treatment in an air jet mill is collision and attrition between particles suspended within a high velocity air stream, which introduces the
15 power to the milling chamber.

The pharmaceutical compositions according to the invention are preferably in the form of pellets or tablets, in particular those which have an enteric coating layer. The pellets can be
20 filled into hard gelatine capsules or sachets which hence also represent preferred embodiments of the composition. The tablets can be prepared from the pellets or from a powder mixture.

25 The pellets preferably comprise

- (a) a core including the pharmaceutically acceptable salt or solvate according to the invention,
- (b) optionally at least one separating layer,
- 30 (c) at least one enteric layer, and
- (d) optionally at least one over-coating layer.

The tablets preferably comprise

- 16 -

- (a) a core including the pharmaceutically acceptable salt or solvate according to the invention,
- (b) optionally at least one separating layer, and
- (c) at least one enteric layer.

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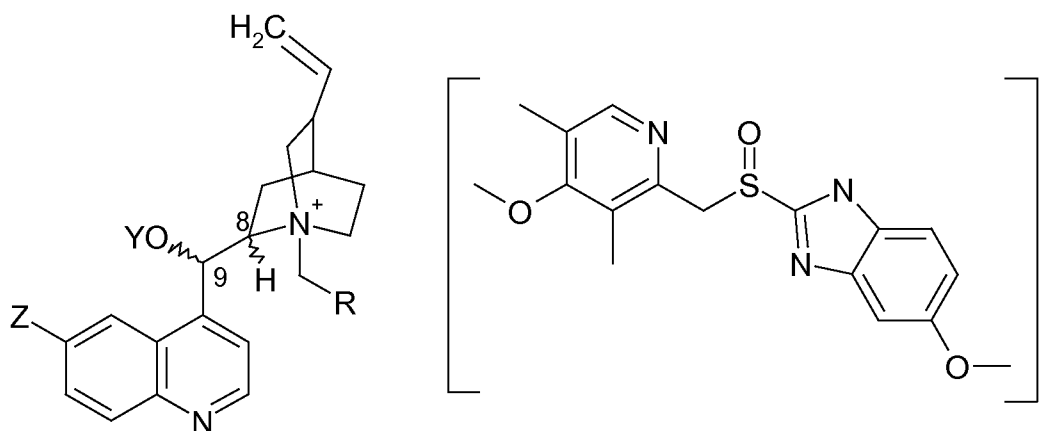
In a preferred embodiment of both, the pellets and the tablets, the pharmaceutically acceptable salt is included in the core in form of a layer covering the core.

- 10 In a further embodiment, the pharmaceutical compositions are in the form of multiple-unit tablets which are obtainable by compressing a mixture of the pellets with tablet excipients.

The present invention also relates to intermediates useful for
15 the preparation of optically pure omeprazole.

According one embodiment of the intermediate, the intermediate is an omeprazole ammonium salt, wherein the ammonium moiety is derived from a chiral amine selected from the group consisting
20 of (-)-brucine, (+)- α -methylbenzylamine, (-)-ephedrine, N,N-dimethylephedrine and bis-(1-phenylethyl)amine.

According to another embodiment of the intermediate, the intermediate is an omeprazole ammonium salt having the formula
25 (II):



- 17 -

(II),

wherein:

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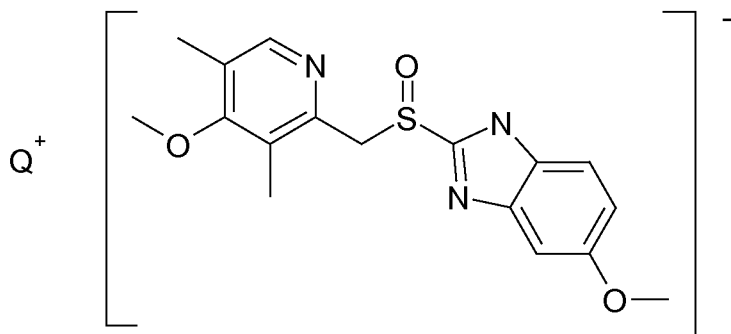
the configuration at C(8), C(9) and the sulfur atom is independently (R) or (S);

Z is hydrogen or methoxy;

Y is benzyl or allyl; and

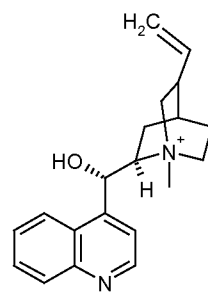
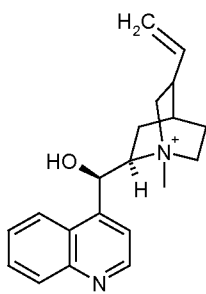
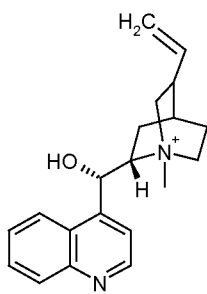
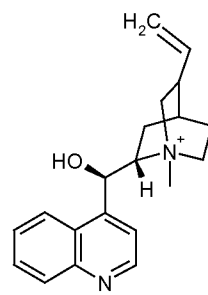
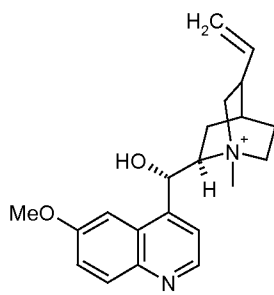
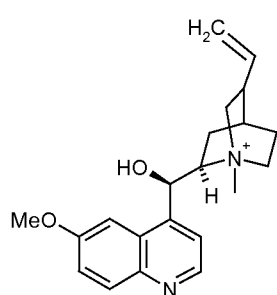
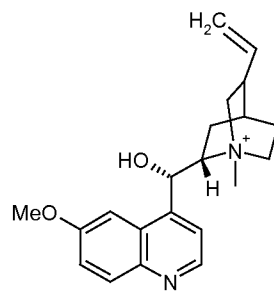
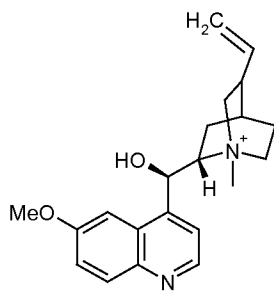
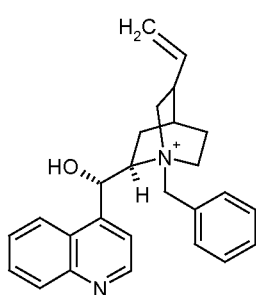
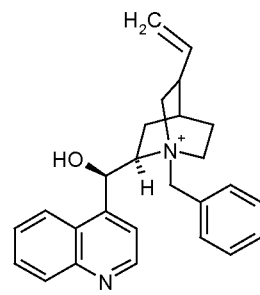
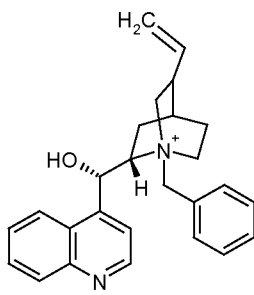
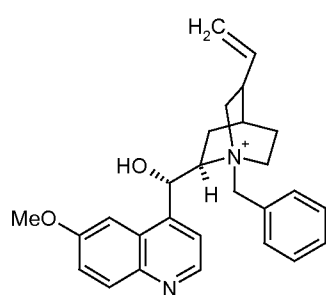
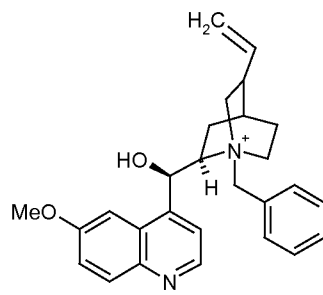
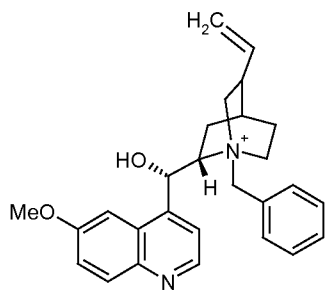
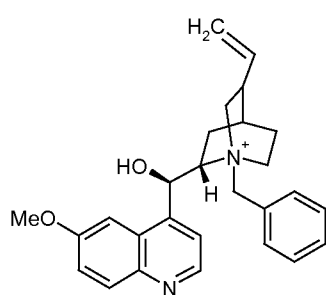
10 R is hydrogen or phenyl.

According to another embodiment of the intermediate, the intermediate is an omeprazole ammonium salt having the formula (III):



(III),

wherein the configuration at the sulfur atom is independently
 20 (R) or (S) and wherein Q^+ is selected from the group consisting of:



General embodiment 2

In another general embodiment, the invention relates to a process for the preparation of enantiomerically enriched omeprazole comprising:

- a.) preparation of racemic or enantiomerically enriched omeprazole;
- 10 b.) treatment of racemic or enantiomerically enriched omeprazole according to a.) by enzyme wherein enantiomerically selective conversion takes place on an atom other than sulfur;
- 15 c.) separation of the obtained mixture comprising enantiomerically enriched omeprazole and derivatives, wherein percentage of enantiomerically enriched omeprazole is different than the percentage of enantiomerically enriched omeprazole in step a.); and
- 20 d.) optionally further purification of enantiomerically enriched omeprazole, preparation of pharmaceutically acceptable salt of enantiomerically enriched omeprazole and optionally preparation of pharmaceutical formulation.

The omeprazole or enantiomerically enriched omeprazole used in the process according to the invention can be prepared according to any desired method, many of which are known to those of ordinary skill in the art. Examples of suitable methods to manufacture omeprazole are given by EP-A-5129, EP-A-124 495, EP-A-533 752, DE-A-40 35 455, EP-A-652 872, EP-A-707 580, EP-A-773 940, EP-A-795 024, EP-A-836 601, EP-A-897 386, EP-A-946 547, EP-A-984 957, EP-A-964 859, EP-A-1 004 305, EP-A-1 095 037, EP-A-1 104 417, EP-A-1 230 237, EP-A-1 409 478, EP-A-1 458 709, WO-A-03/08940, EP-A-1 375 497, WO-A-2004/2982, WO-A-2004/52882, WO-A-2004/87702, EP-A-1 375 497, WO-A-2005/54228 and WO-A-2005/116011.

- 20 -

A ratio of S-(-)-omeprazole and R-(+)-omeprazole in enantiomeric mixture can be changed by enzyme reaction by forming 5-hydroxy and 5-O-desmethyl compounds of the (S)(-)-enantiomer and the (R)(+)-enantiomer of omeprazole. The difference in enzyme kinetic properties between the two enantiomers is used to change the percentage of enantiomerically enriched omeprazole.

According to this general embodiment, an enantioselective formation of 5-hydroxy and 5-O-desmethyl derivatives of the (S)(-)-enantiomer and the (R)(+)-enantiomer of omeprazole is prepared by enzyme reaction. Hepatic cytochrome P450 enzymes can be used, for example hepatic cytochrome P450 enzyme CYP2C19 can be used. Preferably, the enzyme is selected from cytochrome P450 enzyme. A particularly preferred enzyme is CYP2C19.

Enzymes can be selected from recombinant or non-recombinant enzymes. Optionally, the process according to this general embodiment of the invention can be performed by immobilized enzymes or as a whole cell biotransformation.

Omeprazole and its enantiomers are extensively metabolized in the liver by the cytochrome P450 enzyme system. The main metabolites of (S)(-)-enantiomer and the (R)(+)-enantiomer of omeprazole are the 5-hydroxy, 5-O-desmethyl and sulphone metabolites, which are all inactive. The metabolism is mediated primarily by CYP2C19 and CYP3A4 enzymes. However, (S)(-)-enantiomer and the (R)(+)-enantiomer differ in the ratio in which they are metabolized by CYP2C19 and CYP3A4. In vitro experiments using human liver microsomes have shown that (S)(-)-enantiomer is metabolized to a greater extent by CYP3A4 compared with the (R)-isomer, and hence omeprazole, at the same dose, and to a lesser extent by CYP2C19.

- 21 -

Since the oxidation products of (S)(-)-enantiomer and the (R)(+)-enantiomer of omeprazole have different properties than the (S)(-)-enantiomer and the (R)(+)-enantiomer of omeprazole, separation of the obtained compounds by conventional means
5 provide enantiomerically enriched omeprazole and the (S)(-)-enantiomer of a high purity.

The enzyme reaction according to this general embodiment of the invention is carried out in a buffer system. Tris-
10 hydrochloride buffer is preferably used for carrying out the reaction.

A preferred pH of the reaction is in the range of 7 to 9, more preferably in the range 7.2 to 8.0, most preferably in the
15 range 7.3 to 7.5.

A preferred temperature range for carrying out the reaction is in the range of 25 to 45 °C, more preferably in the range of 30 to 40 °C, most preferably in the range of 35 to 39 °C.
20

A preferred reaction is started by adding NADPH, and carried out for a period of time between 0.01 hours and 50 hours, more preferably 0.1 hours and 24 hour, most preferably between 0.1 hours and 10 hours.
25

Preferably, the reaction is stopped by addition of acetonitrile, methanol, butanol, methylene chloride and mixtures thereof.

30 The enantiomerically enriched omeprazole can be further purified with the chromatographic methods disclosed according to general embodiment 3 below.

General embodiment 3

In another general embodiment, racemic or enantiomerically enriched omeprazole and obtained derivatives can be resolved by
5 a chromatography process.

More particularly, racemic or enantiomerically enriched omeprazole can be resolved by the chiral chromatography process described below. Preferably, enantiomerically enriched omeprazole is resolved. Enantiomerically enriched omeprazole enables
10 a process wherein higher loads of omeprazole can be applied in a chromatographic process and wherein (S)(-)-enantiomer of omeprazole is obtained in high purity.

15 A "racemic omeprazole" in the context of this general embodiment of the invention means a mixture of S-(-)-omeprazole and R-(+)-omeprazole in a ratio of 55:45 to 45:55, preferably in a ratio of about 50:50.

20 An "enantiomerically enriched omeprazole" in the context of this general embodiment of the invention means a mixture, wherein the percentage of S-(-)-omeprazole is greater than the percentage of R-(+)-omeprazole. Typically, enantiomerically enriched omeprazole is a mixture of S-(-)-omeprazole and R-
25 (+)-omeprazole in the ratio of 100:0 to 55:45, preferably in the ratio of 100:0 to 60:40, more preferably 100:0 to 70:30.

The stationary phase used in the chiral chromatography process may comprise chiral selectors or stationary phases; batch
30 and/or supercritical-fluid chromatography can be used. Preferably, chiral stationary phases can be selected from polysaccharide-derived chiral stationary phases, such as cellulose tris (3,5-dimethylphenylcarbamate) immobilized on a silica support, amylase tris (3,5-dimethylphenylcarbamate) immobi-
35 lized on a silica support or from the group of stationary

- 23 -

phases of Pirkle type chiral stationary phases, such as π -electron donor/ π -electron acceptors.

Preferably, the stationary phase comprises dimethyl N-3,5-dinitro-benzoyl- α -amino-2,2-dimethyl-4-pentenyl phosphonate covalently bound to mercaptopropyl silica (commercially available as (R) α -Burke[®] and (S) α -Burke[®]); 3,5-dinitrobenzoyl derivative of 1,2-diaminocyclohexane; 3,5-dimethyl phenyl carbamate and tris-(3,5-dimethylphanyl)carbamoyl cellulose.

Preferably, the mobile phase used in the chiral chromatography process comprises an alcohol, another organic solvent, or a mixture thereof. The alcohol may comprise methanol, ethanol, propanol, isopropanol, or a mixture thereof. The organic solvent may comprise acetonitrile, methylenchloride or hexane. Optionally, the mobile phase comprises a mixture of an alcohol with another alcohol or another organic solvent.

Optionally additives such as diethyl amine, triethyl amine or isopropylamine can be added in an amount of 0.01 to 0.5 vol. %, preferably 0.05 to 0.01 vol. %.

II. Pharmaceutically acceptable salts

WO-A-94/27988 discloses certain salts, namely Na⁺, Mg²⁺, Li⁺, K⁺, Ca²⁺ and N(R)₄⁺ salts, wherein R is an alkyl with 1-4 carbon atoms, of the single enantiomer of omeprazole and their preparation. These compounds are said to have improved pharmacokinetic properties which give an improved therapeutic profile, such as a lower degree of variation between individuals taking the compound.

Various other salts of esomeprazole have also become known. WO-A-98/54171 describes magnesium esomeprazole trihydrate; WO-A-00/44744 describes specific polymorphs of the potassium salt

- 24 -

of esomeprazole; WO-A-2003/74514 discloses some primary amine salts of esomeprazole; WO-A-2004/037253 describes certain alkali metal or amine salts of esomeprazole; WO-A-2004/99182 and WO-A-2004/99181 disclose zinc and barium salts of esomeprazole, respectively; EP-A-1 726 305 discloses zinc salts of omeprazole and its enantiomers, WO-A-2005/023796 discloses adamantan ammonium salts of omeprazole and esomeprazole; and WO-A-2005/023797 describes the 1-cyclohexyl ethyl ammonium salt of *inter alia* esomeprazole. EP-A-1 018 340 describes amino acid salt compounds of benzimidazole derivatives and their inclusion complexes with cyclodextrins. The amorphous L-arginine omeprazole salt is described which is produced by spray drying.

15 Pharmaceutically acceptable salts of esomeprazole according to the present invention can be prepared according to any of the described methods. In particular, pharmaceutically acceptable salts can be prepared starting from substantially optically pure or enantiomerically enriched omeprazole prepared by optical resolution according to any of the general and preferred embodiments described herein above. Preferred pharmaceutically salts of esomeprazole according to the present invention are esomeprazole magnesium, esomeprazole arginine and esomeprazole zinc, and solvates thereof.

25 Esomeprazole magnesium solvates can be selected from the group of monohydrate, dihydrate and trihydrate, preferably dihydrate.

30 The pharmaceutically acceptable salts of esomeprazole can be in crystalline form or in amorphous form, and the latter form may facilitate its processing into pharmaceutical compositions.

- 25 -

The pharmaceutically acceptable salts of esomeprazole have been characterized by FT-IR spectrum, X-ray powder diffraction pattern and ^1H -NMR spectrum and analyzed in accordance with the article »Enantioselective Analysis of Omeprazole in Pharmaceutical Formulations by Chiral High-Performance Liquid Chromatography and Capillary Electrophoresis« (J. Braz. Chem. Soc., Vol. 15, No. 2, 318-323, 2004).

FT-IR spectra of KBr discs including the pharmaceutically acceptable salts of esomeprazole according to the invention were recorded over a wave number range of $4000 - 400 \text{ cm}^{-1}$ on a Perkin Elmer Spectrum GX FT-IR spectrometer at a resolution of 4 cm^{-1} .

X-ray powder diffraction patterns were obtained by using a Phillips PW3040/60 X'Pert PRO powder diffractometer; $\text{CuK}\alpha$ radiation $1.541874 \text{ \AA}$.

Crystallinity of esomeprazole and pharmaceutically acceptable salts according to the invention has been characterized according to the method 2.9.33. described in Ph. Eur. 5.6.(2007).

The degree of crystallinity by x-ray powder diffraction (xrpd) has been determined using the formula:

$$\% \text{ crystallinity} = 100 A / (A + B - C)$$

wherein A is total area of the peaks arising from diffraction from the crystalline fraction of the sample; B is total area below area A and C is background area (due to air scattering, fluorescence, equipment, etc).

The pharmaceutically acceptable salts of esomeprazole according to the present invention can have a degree of crystallin-

- 26 -

tiy in the range 0 % to 100 %. Pharmaceutically acceptable salts of esomeprazole of defined degree of crystallinity can be obtained by mixing of pharmaceutically acceptable salt of at least two different degree of crystallinity. Degree of
5 crystallinity is preferably in the range of 50 % to 100 %, most preferably in the range 60 % to 90 %.

Polymorphic form of magnesium esomeprazole dihydrate according to the invention with the degree of crystallinity of 100 % is
10 Form B as defined in Example 5 of EP-B-0 984 957.

The pharmaceutically acceptable salts of esomeprazole prepared according to the present invention can have a purity level of up to 99.9%.

III. Particle size

The particle size of the esomeprazole and pharmaceutically acceptable salts according to present invention is preferably in
20 the range of 0.1-250 microns. If smaller particles are needed, they can be milled or micronized optionally together with other excipients. During this process the mechanical force on the particle surface leads to a particle size reduction. However,
25 it can also release the structure changes of the material. For this purpose an air jet mill, a ball mill or a hammer mill are commonly used as milling equipment. The basic principle of the treatment in an air jet mill is collision and attrition between particles suspended within a high velocity
30 air stream, which introduces the power to the milling chamber.

IV. Pellets and tablets

The pharmaceutical compositions according to the invention are
35 preferably in the form of pellets or tablets, in particular

- 27 -

those which have an enteric coating layer. The pellets can be filled into hard gelatine capsules or sachets which hence also represent preferred embodiments of the composition. The tablets can be prepared from the pellets or from a powder mixture.

The pellets preferably comprise

- (a) a core including the pharmaceutically acceptable salt according to the invention,
- (b) optionally at least one separating layer,
- (c) at least one enteric layer, and
- (d) optionally at least one over-coating layer.

The tablets preferably comprise

- (a) a core including the pharmaceutically acceptable salt according to the invention,
- (b) optionally at least one separating layer, and
- (c) at least one enteric layer.

In a preferred embodiment of both, the pellets and the tablets, the pharmaceutically acceptable salt is included in the core in form of a layer covering the core.

In a further embodiment, the pharmaceutical compositions are in the form of multiple-unit tablets which are obtainable by compressing a mixture of the pellets with tablet excipients.

Further preferred embodiments of pellets and tablets and preferred ways of producing them are described below.

A. Pellets

Preferred pellets comprise a pellet core, optionally a separating coating, an enteric coating and optionally an over-
5 coating as follows.

1. Core

The core is prepared from powders comprising pharmaceutically
10 acceptable salt and at least one pharmaceutically acceptable excipient by extrusion-spheronization or direct pelletization in a high-shear mixer or a rotor granulator.

Alternatively, the core can also be formed by applying a layer
15 containing pharmaceutically acceptable salt to an inert bead. The most preferred bead is one prepared from starch and sucrose, even though beads of other pharmaceutically acceptable excipients may be used, such as microcrystalline cellulose, vegetable gums, waxes and the like. The size of the beads may
20 vary between approximately 0.1 and 2 mm.

A convenient manner of coating the beads with pharmaceutically acceptable salt is the "powder layering" process in centrifugal equipment, i.e. rotor fluid bed equipment (Glatt Rotor
25 Granulator), or a coating pan, i.e. a conventional coating pan (Pellegrini Coating Pan, GS Coating System). The inert beads are moistened with a solution of binder, and then the active substance together with other excipients is added as a powder and the layered pellets are dried in the same equipment in
30 which the coating is performed or other specialized equipment for drying, such as a drying chamber with or without vacuum, is used.

The layer with pharmaceutically acceptable salt can also be
35 formed in the "suspension layering" or "solution layering"

- 29 -

process by spraying the pharmaceutically acceptable salt suspension or solution onto the inert cores in a fluid bed coater granulator. Organic solvents or water can be used during this process.

5

The core, and in particular the layer with the active ingredient, comprises, pharmaceutically acceptable salt, at least one excipient selected from stabilizers, fillers, disintegrating agents, wetting agents, binders or other pharmaceutically acceptable ingredients, alone or in mixtures.

10

The stabilizer is preferably chosen among substances, such as sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids, aluminium hydroxide/sodium bicarbonate coprecipitate, aluminium, calcium and magnesium hydroxides, magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds, sodium lauryl sulphate, zinc hydroxide or hydroxide carbonate, alkaline reacting amino acids, their esters and salts or other similar, pharmaceutically acceptable pH-buffering substances.

15

20

Furthermore, the filler is preferably selected from the group consisting of microcrystalline cellulose, sucrose, starch, lactose, mannitol, sorbitol and mixtures thereof.

25

The disintegrating agent is preferably selected from the group consisting of starch, starch derivatives such as sodium starch glycolate or pregelatinized starch, low-substituted hydroxypropyl cellulose, crospovidone, croscarmellose sodium and mixtures thereof.

30

- 30 -

The wetting agent is preferably selected from the group consisting of sodium dodecyl sulphate, polyoxyethylene sorbitan fatty acid esters, poloxamers and mixtures thereof.

- 5 The binder is preferably selected from the group consisting of polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, methylcellulose and mixtures thereof.

10

2. Separating layer

Before applying the enteric coating layer onto the cores present in form of individual pellets, said pellets may optionally
15 be covered with one or more separating layers comprising pharmaceutical excipients optionally including alkaline compounds, such as for instance pH-buffering compounds. This layer/these layers separate(s) the core material from the outer enteric coating layer. The separating layer can be applied to the core
20 by a coating or layering process in suitable equipment such as a coating pan, coating granulator or in a fluid bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer can be applied to the core by using the powder coating technique. The materials for
25 separating layers are pharmaceutically acceptable compounds, such as sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or
30 in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking agents and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included in the separating layer.

35

The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer can be further strengthened by introducing into the layer substances chosen from a group of compounds usually used in antacid formulations, such as magnesium oxide, hydroxide or carbonate, zinc hydroxide or hydroxide carbonate, aluminium or calcium hydroxide, carbonate or silicate, composite aluminium/magnesium compounds, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitates or similar compounds, or other pharmaceutically acceptable pH-buffering compounds, such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids, or suitable organic bases, including basic amino acids, their esters and salts. Talc or other compounds may be added to increase the thickness of the layer and thereby strengthen the diffusion barrier.

The optionally applied separating layer is not essential for the compositions according to the invention. However, the separating layer may improve the chemical stability of the active substance and/or the physical properties of the final dosage form.

The separating layer may also protect the enteric coating layer towards cracking during a compaction process. For this purpose the separating layer preferably contains pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness. Such plasticizers are for example triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, dimethyl polysiloxan, cetyl alcohol, stearyl alcohol, polyethylene glycols, propylenglycole, polysorbates or other plasticizers. The mechanical properties, i.e. flexibility and hardness of the separating layer are adjusted so that the acid resistance of the pellets covered with

- 32 -

enteric coating layer does not decrease significantly during the compression of pellets into tablets. The amount of plasticizer is usually 10-50 % by weight of the separating layer forming material. Additives such as dispersants, colorants, pigments, polymers, anti-tacking agent and antifoaming agents may also be included into the separating layer. The maximum thickness of the applied separating layer is normally only limited by processing conditions.

3. Enteric layer

One or more enteric coated layers are applied onto the core or onto the core covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents and is preferably comprising a polymer. As enteric coating layer polymers one or more, separately or in combination, of the following can be used: solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s).

The enteric coating layers can also contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness. Such plasticizers are for example those mentioned above under 2. Separating layer. The amount of plasticizer is optimized for each enteric coating layer formula, in relation to the selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the en-

- 33 -

teric coating layer(s) are adjusted so that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during a compression of the pellets into tablets. The amount of plasticizer is usually 10-50 % by weight of the enteric coating layer polymer(s). Additives such as dispersants, colorants, pigments, polymers, anti-tacking agent and antifoaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

To protect an acidic susceptible substance in the form of pharmaceutically acceptable salts of esomeprazole and to obtain an acceptable acid resistance of the multi-unit tableted dosage form, the enteric coating layer(s) usually have a thickness of about at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

4. Over-coating layer

The enteric coated pellets can optionally be covered with one or more over-coating layers. The over-coating layer can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipment, such as a coating pan, a coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. The materials for the over-coating layer are chosen among pharmaceutically acceptable compounds, such as sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pig-

- 34 -

ments, fillers, anti-tacking agents and anti-static agents, such as magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer.

5 The over-coating layer may further prevent potential agglomeration of enteric coating layered pellets and further enhance a subsequent tableting process. The over-coating layer may also protect the enteric coating layer towards cracking during a compaction process. For this purpose the over-coating layer
10 contains pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness. Such plasticizers are for example triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, dimethyl polysiloxan, cetyl alcohol, stearyl alcohol, polyethylene glycols, propylenglycole, polysorbates or other plasticizers. The
15 mechanical properties, i.e. flexibility and hardness of the over-coating layer are adjusted so that the acid resistance of the pellets covered with enteric coating layer does not decrease significantly during a compression of the pellets into
20 tablets. The amount of plasticizer is usually 10-50 % by weight of the over-coating layer forming material. Additives such as dispersants, colorants, pigments, polymers, anti-tacking agent and antifoaming agents may also be included into the over-coating layer. The maximum thickness of the applied
25 over-coating layer is normally only limited by processing conditions.

B. Tablets, prepared from pellets (Multiple unit tablets)

30

The pellets according to the invention can be used for the preparation of multiple unit tablets.

For this purpose the enteric coated pellets with or without an
35 over-coating layer are mixed with tablet excipients, such as

- 35 -

fillers, binders, disintegrating agents, lubricants and other pharmaceutically acceptable additives, and compressed into tablets. The compressed tablet is optionally covered with a film forming agent to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport.

C. Tablets, prepared from powder mixtures

In another preferred embodiment, the pharmaceutical composition is in form of tablets which comprise a tablet core, optionally a separating coating, and an enteric coating.

The preferred composition and the preferred manner for producing such tablets are given hereinafter.

1. Tablet cores

The tablet cores are prepared from powder mixtures comprising the active substance and at least one pharmaceutically acceptable excipient by using the process of direct compression. Alternatively, said tablet cores can also be formed in the process of wet or dry granulation. The tablet cores comprise, besides pharmaceutically acceptable salts of esomeprazole, at least one excipient selected from stabilizers, fillers, disintegrating agents, wetting agents, binders or other pharmaceutically acceptable ingredients, alone or in mixtures.

The stabilizer is preferably chosen among substances such as sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids, aluminium hydroxide/sodium bicarbonate coprecipitates, aluminium, calcium and magnesium hydroxides, magnesium oxide or composite substances such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or

- 36 -

similar compounds, sodium lauryl sulphate, zinc hydroxide or hydroxide carbonate, alkaline reacting amino acids, their esters and salts, or other similar, pharmaceutically acceptable pH-buffering substances.

5

Furthermore, the filler is preferably selected from the group consisting of microcrystalline cellulose, sucrose, starch, lactose, mannitol, sorbitol and mixtures thereof.

10 The disintegrating agent is preferably selected from the group consisting of starch, starch derivatives such as sodium starch glycolate or pregelatinized starch, low-substituted hydroxypropyl cellulose, crospovidone, croscarmellose sodium and mixtures thereof.

15

The wetting agent is preferably selected from the group consisting of sodium dodecyl sulphate, polyoxyethylene sorbitan fatty acid esters, poloxamers and mixtures thereof.

20 The binder is preferably selected from the group consisting of polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, methylcellulose and mixtures thereof.

25

2. Separating layer

Before applying the enteric coating layer onto the tablet cores, said tablet cores may optionally be covered with one or
30 more separating layers comprising pharmaceutical excipients optionally including alkaline compounds, such as pH-buffering compounds. This layer/these layers separate(s) the core material from the outer enteric coating layer. The separating layer can be applied to the core by a coating or layering process
35 in suitable equipment, such as a coating pan, a coating

- 37 -

granulator or in a fluid bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer can be applied to the tablet core by using a suitable coating technique. The materials for separating layers are pharmaceutically acceptable compounds, such as sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking agents and anti-static agents, such as magnesium stearate, titanium dioxide, talc and other additives may also be included into the separating layer.

The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer can be further strengthened by introducing into the layer substances chosen from a group of compounds usually used in antacid formulations, such as magnesium oxide, hydroxide or carbonate, zinc hydroxide or hydroxide carbonate, aluminium or calcium hydroxide, carbonate or silicate, composite aluminium/magnesium compounds, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitates or similar compounds, or other pharmaceutically acceptable pH-buffering compounds, such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids, or suitable organic bases, including basic amino acids, esters and salts thereof. Talc or other compounds may be added to increase the thickness of the layer and thereby strengthen the diffusion barrier. The optionally applied separating layer is not essential for the tablets according to the invention. However, the separating layer may improve the chemical stability of the active substance and/or the physical properties of the tablet.

3. Enteric layer

5 One or more enteric coating layers are applied onto the tablet cores or onto the tablet cores covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents and preferably comprises
10 a polymer. As enteric coating layer polymers one or more, separately or in combination, of the following can be used: solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl
15 acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s).

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, dimethyl polysiloxan, cetyl alcohol, stearyl alcohol, polyethylene glycols, propylenglycole, polysorbates or
25 other plasticizers. The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the
30 mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s) are adjusted. The amount of plasticizer is usually 10-50 % by weight of the enteric coating layer polymer(s). Additives such as dispersants, colorants, pigments, polymers, anti-tacking agent and antifoaming agents
35 may also be included into the enteric coating layer(s). Other

- 39 -

compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

5 To protect an acidic susceptible substance in the form of pharmaceutically acceptable salts of esomeprazole and to obtain an acceptable acid resistance of the tableted dosage form, the enteric coating layer(s) constitutes a thickness of about at least 10 μm , preferably more than 20 μm . The maximum
10 thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

The present invention will further be illustrated by means of
15 the following examples.

ExamplesExample 1

5 The resolution of racemic omeprazole was tested with different chiral amines as resolving agents:

(+)-quinidine, (-)-strychnine, (-)-ephedrine, (-)-brucine,
(-)quinine, (-)-cinchonidine, (+)-hydroquinidine, ((-) or
10 (+))- α -methylbenzylamine, (-)-benzyl- α -methylbenzylamine, (-)-
2-amino-butanol, (+)-2-amino-1-phenyl-1,3-propanediol, ((-) or
(+))-phenylalaninol, (+)-prolinol, ((+) or (-))-1-phenyl-
propylamine, (+)-cinchonine, (+)-benzyl- α -methylbenzyl-amine,
(+)-dehydro-abietyl amine, (-)-2-amino-1-phenyl-1,3-
15 propanediol, (-)-nicotine, (-)-pseudoephedrine, (+)-methyl-
ephedrine.

For each chiral base the following solvents were tested:

75 % acetone, ethanol, 95 % ethanol, methanol, iso-propanol,
20 90 % iso-propanol, iso-butanol, 80 % methanol, water, 75 %
methylethyl ketone, propanol and 85 % propanol.

From the group of tested amines, (+)-quinidine, (-)-brucine,
(-)-cinchonidine and (+)- α -phenylethylamine showed the
25 best results, as seen on Tables 1-4.

General method for preparation of enantiomerically enriched omeprazole:

30 To the tube optically active base was added, approx.
0.0312 mmol. The solution of racemic omeprazole was prepared
by dissolving 6.2 g of omeprazole in 36.0 ml dichlo-
romethane/methanol (2:1) and an aliquot of 62.5 μ l was added
to the tube.

35

- 41 -

After evaporation of the solvent, tube was filled up with appropriate solvent and heated slowly up to 80 °C to ensure clear solution. The solution was allowed to cool to room temperature and then cooled to 0 - 4 °C. From tube solvent was
5 carefully removed and crystals were treated with 500 µl of 1 N sulfuric acid solution. The acidic solution was extracted with 200-300 µl of ethyl acetate. Ethyl acetate layer was sucked off in pre-weighed tube. The solvent was evaporated and tube was weighed. Residue was dissolved in 1 ml of methanol and
10 specific optical rotation was measured.

The results are summarized in Tables 1-4 below. All tests with water or 90 % IPA as a solvent or (-)-pseudoephedrine or (+)-methyl-ephedrine as a resolving agent were negative (no pre-
15 cipitate or $[\alpha]=0^\circ$) and are omitted from the table.

Tables 1-4: Results of resolution of omeprazole with different resolving agents. Empty cell in the table means there was no resolution ($[\alpha]=0^\circ$) or no precipitate.
20

Y = Yield of enantiomerically enriched omeprazole in mg

$[\alpha]$ = specific rotation reading from the digital polarimeter taken at ambient temperature in methanol, $\lambda = 589$ nm.
25

Table 1:

Resolving agent	(+)- Quinidine	(-)- Strychnine	(-)- Ephedrine	(-)- Brucine	(-)- Quinine	(-)- Cinchonidine
solvent						
75% acetone						Y = 2.4 [α] = +1.25
EtOH	Y = 2.0 [α] = +26.5	Y = 2.4 [α] = +1.66	Y = 6.0 [α] = +2.33			Y = 6.1 [α] = -4.0
95% EtOH		Y = 7.4 [α] = +0.945				
MeOH	Y = 6.5 [α] = +11.23				Y = 8.8 [α] = -0.45	
IPA	Y = 10.9 [α] = -2.75			Y = 9.9 [α] = +13.1		Y = 11.2 [α] = +0.66
i-butanol	Y = 5.9 [α] = +1.02				Y = 8.2 [α] = +9.14	Y = 13.1 [α] = +24.4
80% MeOH	Y = 2.9 [α] = +4.82	Y = 4.2 [α] = +1.19				
75% MEK		Y = 2.3 [α] = +0.869				Y = 15.6 [α] = +11.9
propanol	Y = 4.3 [α] = +1.39	Y = 13.7 [α] = -0.29		Y = 5.1 [α] = +0.98	Y = 4.5 [α] = +12.4	Y = 4.5 [α] = +1.33
85 % propanol		Y = 1.8 [α] = -1.11				Y = 4.1 [α] = -1.70

Table 2:

Resolving agent	(+)-Hydroquinidine	(+)- α -methylbenzylamine	(-)-Benzyl- α -methylbenzyl-amine	(-)-2-amino-butanol	(+)-2-amino-1-phenyl-1,3-propanediol
solvent					
75% acetone					
EtOH		Y=2.5 [α]= -4.80	Y=1.2 [α]= -7.69		Y=2.8 [α]= -3.21
95% EtOH					
MeOH	Y=5.8 [α]=+11.6				
IPA					
i-butanol	Y=13.5 [α]=+15.5	Y=1.2 [α]=+26.7	Y=0.6 [α]=+8.33	Y=0.9 [α]= -4.44	Y=0.6 [α]=+21.7
80% MeOH	Y=3.5 [α]=+3.71				
75% MEK					
propanol					
85 % propanol					

Table 3:

Resolving agent solvent	(-)-phenyl- alaninol	(+)-prolinol	(+)-phenyl- propyl- amine	(+)- cinchonine	(-)- α - methyl- benzyl- amine	(+)-benzyl- α -methylben- zyl amine
75% ace- tone				Y=1.2 [α]=+20.8		
EtOH	Y=2.7 [α]= -7.03	Y=2.7 [α]= -0.79	Y=2.4 [α]= -6.66	Y=0.9 [α]= -7.77	Y=0.9 [α]= -14.4	Y=1.9 [α]= -4.21
95% EtOH				Y=3.1 [α]= -1.29	Y=3.4 [α]= -4.11	Y=5.7 [α]= -1.75
MeOH				Y=1.8 [α]=+10.0		
IPA			Y=1.0 [α]=+9.0	Y=1.3 [α]=+2.30		Y=2.2 [α]= -4.54
i-butanol	Y=1.0 [α]= -11.0		Y=0.3 [α]= -10.0	Y=1.2 [α]=+5.00		Y=1.0 [α]=+3.0
80% MeOH				Y=1.2 [α]=+0.833		
75% MEK				Y=0.8 [α]= -3.75		
propanol			Y=0.4 [α]= -22.5			Y=3.7 [α]= -1.89
85 % pro- panol						

Table 4:

Resolving agent	(+)-dehydro-abietylamine	(-)-2-amino-1-phenyl-1,3-propanediol	(-)-nicotine	(+)-phenyl-alaninol	(-)-1-phenyl-propalamine
solvent					
75% acetone					
EtOH	Y=7.3 [α]=+10.0	Y=0.8 [α]= -13.8		Y=1.9 [α]= -2.63	Y=1.5 [α]= -6.66
95% EtOH	Y=9.1 [α]=+10.1		Y=2.4 [α]= -2.91		Y=1.5 [α]= -9.33
MeOH					
IPA		Y=9.0 [α]= -1.66	Y=7.9 [α]= -1.64	Y=1.8 [α]= -5.55	Y=1.0 [α]= -8.00
i-butanol	Y=18.2 [α]=+3.02	Y=2.9 [α]= -7.00	Y=14.5 [α]=+0.827	Y=2.6 [α]= -0.46	Y=1.0 [α]= -14.0
80% MeOH					Y=3.1 [α]= -2.90
75% MEK					
propanol	Y=3.4 [α]=+7.05	Y=4.8 [α]= -0.416		Y=18.6 [α]= -0.913	Y=3.1 [α]= -1.61
85 % propanol					

Example 2

Optical resolution of racemic omeprazole

5 To a solution of omeprazole (5.92 g) in 200 ml of methanol, a methanolic solution of N-benzylcinchoninium hydroxide (7.2 g in 100 ml MeOH) was added. After stirring the mixture at room temperature for 0.5 hours, the solution was evaporated in vacuo to dryness at a temperature of 45°C. The resulting pale
10 yellow solid of diastereomeric pair salt (13.2 g, m.p. 183-186°C) was twice recrystallized from n-butanol/2-propanol (1:7) to give 5.2 g of (S)-omeprazole N-benzylcinchoninium salt (m.p. 205-207°C, 99% d.e. determined by chiral HPLC). A second crop (0.7 g, m.p. 202-204°C, 98.5% d.e. determined by
15 chiral HPLC) was obtained by concentrating the combined mother liquor and washings, and twice allowing recrystallization to proceed at room temperature for 24 hours.

The obtained salt (5.2 g) was dissolved in a mixture of 25 ml of ethanol and 2.5 ml of water. To the solution was added
20 0.3 N hydrochloric acid solution under stirring in an ice bath to a pH value of 3-3.5, and the mixture was stirred at a temperature of 0°C for 1 hour. The solvent was evaporated in vacuo to give a semisolid mass, to which 20 ml of ethyl acetate were added. After stirring the mixture at room temperature,
25 the solid was filtered off. N-Benzylcinchoninium chloride was thus recovered in a yield of 99 % having a purity of 99 % (determined by HPLC).

The organic layer was separated and evaporated, and the obtained solidified mass was recrystallized from toluene-
30 cyclohexane (1:3) to give 2.1 g of (S)-omeprazole (m.p. 65-80°C, 99 % e.e. (determined by chiral HPLC), $[\alpha] -41.5^\circ$ (0.17, methanol)).

Example 3

Optical resolution of racemic omeprazole

5 A solution of N-benzylcinchoninium chloride (5.9 g) in ethanol/water (9:1, 100 ml) was passed through an Ambersep 900 OH (11 g) column. To the obtained solution omeprazole (4.6 g) was added. After stirring the mixture at room temperature for 1 hour, the mixture was evaporated in vacuo to dryness at a temperature of 45°C. To the obtained solid mass was then added
10 toluene (20 ml), and the resulting mixture was evaporated to dryness. The resulting pale yellow solid (9.7 g) was dissolved in 114 ml of n-butanol/2-propanol (1:7).

After stirring the mixture at room temperature overnight,
15 crystals deposited out therein were obtained through a filtration to give 4.7 g of enriched (S)-omeprazole N-benzylcinchoninium salt.

The material was twice recrystallized from n-butanol/2-propanol (1:7) to give 3.3 g of (S)-omeprazole N-benzylcinchoninium salt (m.p. 203-205°C, 98.5% d.e. (determined by chiral HPLC), $[\alpha] +52^\circ$ (1.0, methanol)).
20

By concentrating the mother liquor and washings and allowing recrystallization to proceed at room temperature for 24 hours, 0.6 g of (S)-omeprazole N-benzylcinchoninium salt was recovered.
25

The obtained salt (3.2 g) was dissolved in 25 ml of ethanol. To the solution was added Dowex 50W, H⁺ form under stirring in an ice bath to a pH value of 4, and the mixture was stirred at a temperature of 0°C for 0.5 hours. The reaction mixture was
30 filtered, washed with 2 x 5 ml of ethanol, and the filtrate was evaporated in vacuo to give a semisolid mass. Solidified mass was recrystallized from toluene/cyclohexane (1:3) to give 0.85 g of (S)-omeprazole (99.5% e.e. (determined by chiral HPLC)).

Example 4

Optical resolution of racemic omeprazole

5 To a mixture of omeprazole (0.79 g) and sodium hydroxide (0.11 g) in methanol (35 ml) a solution of N-methylcinchonidinium iodide (1.0 g) in methanol (30 ml) was added. After stirring the mixture at room temperature for 1 hour, the mixture was cooled down in a refrigerator, filtered (Celite)
10 and then evaporated in vacuo to dryness. The resulting pale yellow solid (m.p. 106-110°C, $[\alpha]$ -65° (1.0, methanol)) was dissolved in 82 ml of acetone/butyl acetate (7:1). After stirring the mixture at room temperature overnight, crystals deposited out therein were obtained through a filtra-
15 tion to give 0.7 g, of enriched (R)-omeprazole N-methylcinchonidinium salt. The material was recrystallized from acetone/butyl acetate (7:1) to give 0.5 g of enriched (R)-omeprazole N-methylcinchonidinium salt (m.p. 193-196°C, $[\alpha]$ -47° (1.0, methanol)).
20 (S)-omeprazole N-methylcinchonidinium salt was obtained from the concentrated mother liquor, i.e. the filtrate after filtration of the crystalline mass. The crystalline (S)-omeprazole N-methylcinchoninium salt was
25 twice recrystallized from 2-butanone/butylacetate (1:3) and a small volume of ethanol; m.p 95-107°C, 98.5% d.e. (determined by chiral HPLC). Liberation of (S)-omeprazole was accomplished analogously to example 3.

30

Example 5

Optical resolution of racemic omeprazole

5 Analogously to example 3, a dimethylformamide solution of N-methylcinchoninium iodide was used.
After stirring the reaction mixture at room temperature for 1 hour, the mixture was evaporated in vacuo to dryness and then washed with diethyl ether (2 x 20 ml) to obtain a pale yellow
10 solid (m.p. 118-129°C, $[\alpha]$ +104° (1.0, methanol)).
The resulting salt was twice recrystallized from 2-butanone and a small volume of ethanol to obtain crystalline (S)-omeprazole N-methylcinchoninium salt (m.p. 110-125°C, 99% d.e. (determined by chiral HPLC), $[\alpha]$ +21° (0.7, methanol)). To a
15 suspension of the obtained salt (2.5 g) in toluene (70 ml) was added 3% aqueous hydrochloric acid at a temperature of 5-10°C to a pH value of 3. The mixture was stirred, filtered and the organic phase was decanted. The organic phase was extracted with 10 % sodium hydroxide solution (2 x 10 ml) and after
20 cooling to 5°C acidified with glacial acetic acid with vigorous stirring. Stirring was continued for 0.5 h, then the solution was seeded with (S)-omeprazole (100 mg) at 5°C and filtered. The collected solid was washed with water (2 x 5 ml) and dried in vacuo at ambient temperature to afford (S)-
25 omeprazole (0.95 g, 99% e.e.) as a slightly brown solid.

Example 6

30 Optical resolution of racemic omeprazole

Analogously to the example 2, a tetrahydrofuran/water (4:1) solution of N-benzylquinidine hydroxide was used.
After stirring the reaction mixture at room temperature for 1
35 hour, the mixture was evaporated in vacuo at a temperature of

- 50 -

45°C. The resulting pale yellow solid was washed with diethyl ether (210 ml) and then filtered (m.p. 80-105°C, $[\alpha]$ +93° (1.0, methanol)).

The crystalline (S)-omeprazole N-benzylquinidinium salt crystallized slowly from 2-butanone/diisopropylether (1:3) and a small volume of ethanol; m.p. 110-125°C, 98% d.e. (determined by chiral HPLC).

10 Example 7

Preparation of (R,S)-omeprazole N-benzylquinine salt

To a solution of omeprazole (2.1 g) in dichloromethane (150 ml) a solution of sodium hydroxide (0.26 g) in water (7.5 ml) was added. To the resulting clear two phase system was added N-benzylquininium bromide (3 g), and the reaction mixture was stirred for 0.5 hours. The organic phase was separated and evaporated in vacuo to dryness at a temperature of 45°C. The obtained pale yellow solid was filtered and washed on a Büchner funnel with hot toluene (2 x 10 ml) to give the diastereomeric pair of omeprazole N-benzylquinine salt (4.7 g, m.p. 106-118°C).

25 Example 8

Preparation of (R,S)-omeprazole N,N-dimethylephedrinium salt

30 Analogously to example 7, N,N-dimethylephedrinium bromide was used.

The diastereomeric pair of omeprazole N,N-dimethylephedrinium salt (m.p. 104-116°C, $[\alpha]$ -13° (1.0, methanol)) was obtained as a pale yellow solid.

Example 9

Preparation of (R,S)-omeprazole O-allyl-N-benzylcinchonidinium salt

5

Analogously to example 4, O-allyl-N-benzylcinchonidinium bromide was used.

The diastereomeric pair of omeprazole O-allyl-N-benzylcinchonidinium salt (m.p. 85-106°C) was obtained as a pale yellow solid.

10

Example 10

15 Preparation of (R,S)-omeprazole N-methylquininium salt

Analogously to example 2, an aqueous quinine methohydroxide solution prepared according J. Am. Chem. Soc. 1941, 63, 1368 was added to the methanol solution of (R,S)-omeprazole.

20

Example 11

Further purification of enantiomerically enriched omeprazole by preparative HPLC

5

Batch	1	2	3	4
Equipment	Preparative Knauer HPLC System			
Data evaluation	Eurochrome			
Feed (S:R)	98:2	95:5	80:20	50:50
Column	"Amy Coat", Kromasil; 10 µm; 150X4,6 mm			
Mobile phase	Methanol + 0.1% Diethylamine (DEA)			
Sample preparation	concentration 30mg/ml esomeprazole in Methanol + 0,1% DEA			
Sample loading (mg/run)	24	32	24	6
Post run	0 min			
Column temperature	25°C			
Flow rate	1.5 mL/min			
Detection	254 nm; 300 nm			
Injection volume	from 0.1 to 4.5ml per run			
Yield, purity (S)	13.18	22.90	11.72	1.4
(mg, % S)	100	99.55	99.73	99.92

Example 12

Preparation of amorphous (S)-omeprazole magnesium

5 *Variant (a)*

50.0 g (0.1447 moles) (S)-omeprazole was dissolved in 500 ml water with 18 ml diethylamine. A solution of 31.47 g (0.0759 moles) magnesium gluconate in 200 ml water was gradually added, and the mixture was stirred for 3 hours at 20-25°C. The product was filtered and washed with 100 ml of water. The wet product was macerated in 500 ml water, filtered and dried to obtain 40.0 g of (S)-omeprazole magnesium as amorphous form.

Variant (b)

50 g (0.1447 moles) (S)-omeprazole was dissolved in 500 ml of water with 18 ml diethylamine. A solution of 13.32 g (0.0723 moles) magnesium bromide in 200 ml of water was gradually added, and the mixture was stirred for 12 hours at 20-25°C. The product was filtered and washed with 100 ml of water. The wet product was macerated in 500 ml water, filtered and dried to obtain 45.0 g of (S)-omeprazole magnesium as amorphous form.

Variant (c)

5.0 g (0.01447 moles) (S)-omeprazole was dissolved in a solution of 50 ml water and 2.52 g (0.01447 moles) arginine. A solution of 1.33 g (0.0072 moles) magnesium bromide in 20 ml water was gradually added, and the mixture was stirred for 12 hours at 20-25°C. The product was filtered and washed with 10 ml of water. The wet product was macerated in 50 ml water, filtered and dried to obtain 4.6 g of (S)-omeprazole magnesium as amorphous form.

Example 13

Preparation of (S)-omeprazole magnesium trihydrate.

5 Magnesium (0.10 g) was activated with iodine and reacted with absolute methanol (10 ml) to give a solution. Reaction mixture was diluted with methanol (15 ml) and added dropwise to a solution of (S)-omeprazole (2.6 g) in methanol (80 ml) for 30 min at 10°C. To the reaction mixture methanol was added (75%
10 water solution, 15 ml) and then filtered clear (Celite) and concentrated by evaporation under reduced pressure. Evaporation gave a white solid of the (S)-omeprazole magnesium trihydrate (m.p. 198-201°C).

15

Example 14

Particle size of (S)-omeprazole magnesium dihydrate form A

20 Starting from (S)-omeprazole obtained according to the process of the present invention, (S)-omeprazole magnesium dihydrate form A was prepared according to example 6 of WO-A-98/54171.

In one variant, the (S)-omeprazole magnesium dihydrate form A
25 was dried without subsequent milling. According to another variant, the (S)-omeprazole magnesium dihydrate form A was milled on Fitz D6A at 2000 rpm. According to a third variant, the (S)-omeprazole magnesium dihydrate form A was dried using a fluid bed apparatus.

30

The mean particle size, particle size distribution and specific surface area obtained according to the three variants are given in the following table:

	unmilled	milled	fluid bed
mean particle size	153 μm	30 μm	9 μm
d ₁₀	12,6 μm	8,3 μm	3,1 μm
d ₅₀	80,5 μm	24,3 μm	7,2 μm
d ₉₀	403,8 μm	60,2 μm	15,3 μm
Specific surface area	6,1 m ² /g	7,7 m ² /g	8,0 m ² /g

The d_x value indicates that a certain percentage X by volume of the particles has a size below a certain limit. For example, a d₉₀ value of 150 μm means that 90 % by volume of the particles have a diameter below 150 μm .

Figure 1 depicts particle size distribution diagrams of unmilled and milled (S)-omeprazole magnesium dihydrate form A.

PHARMACEUTICAL FORMULATIONS WITH (S)-OMEPRAZOLE MAGNESIUM DIHYDRATE FORM A

Example 15

ingredients	composition [g]	percentage
Core material		
(S)-omeprazole magnesium dihydrate form A	41.29*	31.95 %
Neutral spheres	71.16	55.06%
Povidone	15.00	11.61 %
Sodium lauryl sulfate	1.80	1.39 %

- 56 -

Separating layer 1		
Core material	129.25	82.90 %
Opadry II White (PVA, talc, TiO ₂ , PEG) (I)	18.75	12.03 %
Magnesium hydroxide carbonate heavy (I)	7.92	5.08 %

Separating layer 2		
Core material	155.92	89.22 %
Opadry II White (PVA, talc, TiO ₂ , PEG) (II)	18.75	10.73 %
Magnesium hydroxide carbonate heavy (II)	0.08	0.05 %

Enteric coating		
Pellets with separating layer	174.75	69.48 %
Methacrylic acid ethyl acrylate copolymer	62.91	25.01 %
Glycerol monostearate	3.15	1.25 %
Triethyl citrate	9.44	3.75 %
Polysorbate 80	1.26	0.50 %

*mass of (S) - omeprazole magnesium excluding water

- 5 The drug suspension was prepared by suspending (S)-omeprazole magnesium dihydrate form A, which had been obtained according to the invention, into an aqueous solution of povidone and sodium lauryl sulfate. Suspension layering of neutral pellets (e.g. sugar or microcrystalline spheres) was performed in a fluid bed processor using a bottom spray technique (Wurster column) at a batch size of 3.0 kg. The spray operation was stopped when the specified amount of bulk liquid had been sprayed.
- 10

- 57 -

The prepared core material was dried until the loss on drying of the pellets was about 1-1.5 %. The pellets were then covered with two separating layers in a Wurster column. The suspensions used for preparing the separating layers both consisted of purified water, magnesium hydroxide carbonate heavy and Opadry powder mixture, the latter being composed of polyvinyl alcohol, talc, titanium dioxide and polyethylene glycol. The coated pellets were dried until the loss on drying was about 1-1.5 %.

10 An enteric coating suspension was prepared using methacrylic acid ethyl acrylate copolymer (Eudragit L 30 D-55), triethyl citrate, glyceryl monostearate and Polysorbate 80. The suspension was sprayed onto the pellets in a fluid bed apparatus. The spray operation was stopped when the specified amount of bulk liquid had been sprayed, and then drying was carried out in the Wurster column.

The obtained pellets were filled into hard gelatine capsules.

20 Example 16

ingredients	composition [g]	composition [%]
Core material		
(S)-omeprazole magnesium dihydrate form A	41.29*	31.94 %
Neutral (sugar based) spheres	71.15	55.04 %
Povidone	15.03	11.63 %
Sodium lauryl sulfate	1.80	1.39

- 58 -

Separating layer		
Core material	129.27	89.92 %
Methylcellulose	8.00	5.56 %
Magnesium hydroxide carbonate heavy	6.50	4.52 %

Enteric coating		
Pellets with separating layer	143.77	73.21 %
Methacrylic acid ethyl acrylate copolymer	43.13	21.96 %
Glycerol monostearate	2.16	1.10 %
Triethyl citrate	6.47	3.29 %
Polysorbate 80	0.86	0.44 %

*mass of (S) - omeprazole magnesium excluding water

5 The drug suspension was prepared by suspending (S)-omeprazole magnesium dihydrate form A, which had been obtained according to the invention, into an aqueous solution of povidone and sodium lauryl sulfate. Suspension layering of sugar spheres was performed in a fluid bed processor using a bottom spray technique (Wurster column) at a batch size of 3.0 kg. The spray operation was stopped when the specified amount of bulk liquid had been sprayed.

10 The prepared core material was dried until the loss on drying of the pellets was about 1-1.5 %. The pellets were then covered with a separating layer in a Wurster column. The suspension used for forming the separating layer consisted of purified water, methylcellulose and magnesium hydroxide carbonate heavy.

15 The enteric coating suspension was prepared using methacrylic acid ethyl acrylate copolymer (Eudragit L 30 D-55), triethyl citrate, glyceryl monostearate and Polysorbate 80. The suspen-

- 59 -

sion was sprayed onto the pellets in a fluid bed apparatus. The spray operation was stopped when the specified amount of bulk liquid had been sprayed, and then drying was carried out in the Wurster column.

- 5 The obtained pellets were filled into HPMC capsules.

Example 17

ingredients	composition [g]	composition [%]
Core material		
(S)-omeprazole magnesium dihydrate form A	41.29*	36.87 %
Cellactose	56.56	50.50 %
Microcrystalline cellulose	8.47	7.56 %
Croscarmellose sodium	3.43	3.06 %
Magnesium stearate	2.25	2.01 %

Separating layer		
Core material	112.00	88.53 %
Methylcellulose	11.10	8.77 %
Titanium dioxide	0.39	0.31 %
Iron Oxide Yellow	0.07	0.06 %
Propyleneglycol	2.95	2.33 %

Enteric coating		
Tablets with separating layer	126.51	92.67 %
Methacrylic acid ethyl acrylate copolymer	6.78	4.97 %
Macrogol	0.68	0.50 %
Talc	2.54	1.86 %

*mass of (S) - omeprazole magnesium excluding water

The direct compression technology was used to produce tablet cores. The cores were then coated with separating and enteric coating.

5

Example 18

ingredients	composition [g]	composition [%]
Core material		
(S)-omeprazole magnesium dihydrate form A	41.29*	31.33 %
Neutral (sugar based) spheres	71.15	54.00 %
Povidone	15.03	11.41 %
Sodium lauryl sulfate	1.80	1.37 %
Magnesium hydroxide carbonate heavy	2.50	1.90 %

Separating layer		
Core material	131.77	85.42 %
Methylcellulose	8.00	5.19 %
Magnesium hydroxide carbonate heavy	6.50	4.21 %
Povidone	3.00	1.94 %
Talc	5.00	3.24 %

- 61 -

Enteric coating		
Pellets with separating layer	154.27	73.21 %
Methacrylic acid ethyl acrylate copolymer	46.28	21.96 %
Glycerol monostearate	2.31	1.10 %
Triethyl citrate	6.94	3.29 %
Polysorbate 80	0.92	0.44 %

*mass of (S) - omeprazole magnesium excluding water

5 The drug suspension was prepared by suspending (S)-omeprazole magnesium dihydrate form A, which had been obtained according to the invention, into an aqueous solution of povidone and sodium lauryl sulfate. Suspension layering of sugar spheres was performed in a fluid bed processor using a bottom spray technique (Wurster column) at a batch size of 3.0 kg. The spray operation was stopped when the specified amount of bulk liquid had been sprayed.

10 The prepared core material was dried until the loss on drying of the pellets was about 1-1.5 %. The pellets were then covered with a separating layer in a Wurster column. The suspension used for preparing the separating layer consisted of purified water, methylcellulose and magnesium hydroxide carbonate heavy.

15 The enteric coating suspension was prepared using methacrylic acid ethyl acrylate copolymer (Eudragit L 30 D-55), triethyl citrate, glyceryl monostearate and Polysorbate 80. The suspension was sprayed onto the pellets in a fluid bed apparatus. The spray operation was stopped when the specified amount of bulk liquid had been sprayed, and then drying was carried out in the Wurster column.

25

Example 19

Preparation of (S)-omeprazole magnesium dihydrate form A from racemate

5

18.5 ml of a solution of racemic omeprazole (555 mg, 1.61 mmol, chromatographic purity > 98 %) in a 0.1 % solution of diethylamine in methanol (30 mg/ml) was injected into a preparative HPLC system (Column: AmyCoat, Kromasil, 10 μ m, 10 150X50 mm; mobile phase: 0.1 % solution of diethylamine in methanol). The procedure was repeated 13 times (total: 7.2 g of racemate, 3.6 g of (S)-omeprazole) and the fractions containing (S)-omeprazole were collected. The assay of (S)-omeprazole in the solution (99.4 % ee) was determined (HPLC; 15 2.6 g, 7.53 mmol in 1890 ml) and an equivalent amount of a methanolic solution of magnesium methoxide (4.1 ml, 9.6 % solution, 3.76 mmol) was added. The solution obtained after magnesium methoxide addition was evaporated at 54 °C at reduced pressure to obtain an oily residue (3.29 g). The oily residue 20 was dissolved in 6 ml of methanol at room temperature, and then 27 ml of an acetone/water mixture (4:1, v/v) was gradually added to the solution so that the temperature did not exceed 25 °C. The suspension was stirred for 12 hours at 20 $\pm$ 2 °C, then 3 hours at 0 - 5 °C, filtered and washed with 3 ml 25 of acetone.

3.3 g of wet product of crystal form F or G was dried at reduced pressure at temperature from 20 to 40 °C for about 6-10 hours following up to 60-70 °C for 1-2 hours. During the drying 30 form F or G is transformed to magnesium esomeprazole dihydrate form A. 1.91 g of dry product was obtained (yield: 49 %).

Figure 2 depicts an X-ray powder diffraction pattern (Phillips PW3040/60 X'Pert PRO powder diffractometer; CuK α radiation 35 1.541874 Å) of magnesium esomeprazole form F.

Figure 3 depicts an X-ray powder diffraction pattern (Phillips PW3040/60 X'Pert PRO powder diffractometer; CuK α radiation 1.541874 Å) of magnesium esomeprazole form G.

5

Example 20

Preparation of (S)-omeprazole magnesium dihydrate form A from enriched enantiomeric mixture

10

33 ml of solution of enriched enantiomeric mixture of omeprazole ((S)/(R) = 80:20; 1 g, 2.89 mmole) in 0.1 % solution of diethylamine in methanol (30 mg/ml) was injected into a preparative HPLC system (Column: AmyCoat, Kromasil, 10 μ m, 150X50 mm; Mobile phase: 0.1 % solution of diethylamine in methanol). The procedure was repeated 5 times (total: 5 g of racemate; 3.864 g of (S)-omeprazole) and the fractions containing (S)-omeprazole were collected. The assay of (S)-omeprazole in the solution (98.5 % ee) was determined (HPLC; 15 1.32 g, 3.82 mmol in 880 ml) and an equivalent amount of methanolic solution of magnesium methoxide (2.1 ml, 9.6 % solution; 1.9 mmol) was added. The solution obtained after magnesium methoxide addition was evaporated at 50 °C at reduced pressure to obtain an oily residue (1.54 g). The oily residue 25 was dissolved in 3 ml of methanol at room temperature, and then 13 ml of an acetone/water mixture (4:1, v/v) was gradually added to the solution so that the temperature did not exceed 25 °C. The suspension was stirred for 12 hours at 20 $\pm$ 2 °C, then 3 hours at 0 - 5 °C, filtered and washed with 30 1.5 ml of acetone.

Wet product was dried at reduced pressure at temperature from 20 to 40°C for about 6-10 hours following up to 60-70°C for 1-2 hours. 0.87 g of dry magnesium esomeprazole dihydrate form A 35 was obtained (yield: 18 %).

Example 21.i.

Purification of S-(-)-omeprazole from racemic solution by chromatography

Racemic omeprazole was subjected to preparative chromatography using (R) α -Burke column as the stationary phase and methanol as the mobile phase. Using these conditions R-(+)-omeprazole is the more retained component and will elute after S-(-)-omeprazole.

Chromatographic conditions:

Column: (R) α -Burke 2, 16 μ m, 100Å, 250X21.1mm

Mobile phase: Methanol 100%

Load: 275 mg of racemic omeprazole (50:50) dissolved in 11ml MeOH

Flow rate: 42 ml/min

Detection: UV 300 nm

Temperature: RT

Fractions containing S-(-)-omeprazole were collected and 137.5 mg of S-Omeprazole (95.7% pure) was obtained.

Example 21.ii.

Purification of S-(-)-omeprazole from enantiomerically enriched omeprazole solution by chromatography

Enantiomerically enriched omeprazole (ratio 70:30) was subjected to preparative chromatography using (R) α -Burke column as the stationary phase and methanol as the mobile phase. Using these conditions R-(+)-omeprazole is the more retained component and will elute after S-(-)-omeprazole.

- 65 -

Chromatographic conditions:

Column: (R) α -Burke 2, 16 μ m, 100Å, 250X21.1mm

Mobile phase: Methanol 100%

Load: 300mg of enriched mixture (S:R=70:30) dissolved in 11ml
5 of MeOH

Flow rate: 42 ml/min

Detection: UV 300 nm

Temperature: RT

10 Fractions containing S-(-)-omeprazole were collected and 207
mg of S-Omeprazole (99.1% pure) was obtained.

Example 22

15

Enantioselective formation of 5-hydroxy and 5-O-desmethyl de-
rivatives of omeprazole

20 A racemic mixture of omeprazole was dissolved in methanol and
sequentially diluted with 40% of methanol in 0.1 M Tris-
hydrochloride buffer, pH 9. Solution of racemic omeprazole
and enzyme (rCYP2C19) was added to 0.1 M Tris-hydrochloride
buffer (pH 7.4)(final volume 200 μ l). The final pH value of
25 the incubation mixture was kept at 7.4 and the methanol con-
centration was less than 1%. After 5 min preincubation NADPH
(1mM) was added. Reaction was conducted at 37°C for 20 min. The
reaction was terminated by the addition of an aliquot of 100 μ l
of ice-cold acetonitrile and centrifugated (4500g for 20 min).

30 A racemic mixture of omeprazole, rCYP2C19 and 1 mM NADPH dis-
solved in 0.1 M Tris-hydrochloride buffer, pH 7.4, was prepared
(volume of 200 μ l). The reaction started by addition of NADPH
after a preincubation of 5 min at 37°C. Reaction was conducted
at 37°C for 20 min.

35

Example 23

Enantiomeric enrichment of S-(-)-omeprazole from racemic omeprazole through transition metal complex

5

An amount of 10.0 g of omeprazole was suspended in 100 ml of acetone, 1.16 g of sodium hydroxide was added and heated to 35-40 °C.

- 10 An amount of 4.96 g of (2S,3S)-(-)-diethyl tartrate and 4.3 ml of titanium(IV) isopropoxide was added followed by 12 ml of triethylamine to dissolve the mixture. 5.04 g of (S)-(+)-mandelic acid was added, stirred for 2 hours, cooled to room temperature and filtered the salt, washed with 50 ml of acetone. The wet product was dried to obtain 12.5 g (S:R=70:30).
15 The hot slurrying (4g in 50 ml acetone) at 50 -55°C for 2 hours gives 2.7 g of salt with 94:6 (S:R).

- An amount of 7.7 g of esomeprazole mandelic acid salt was suspended in 80 ml of methylene chloride, 80 ml of 5% aqueous sodium bicarbonate was added and organic layer was separated and concentrated to obtain 4.6 g of oil product.
20

25 Example 24

Preparation of magnesium salt of S-(-)-omeprazole (magnesium esomeprazole)

- 30 An amount of 7.75 esomeprazole was dissolved in 150 ml of aqueous solution of sodium hydroxide (0.6%) at 25-30 °C, filtered to get a clear solution. To this solution 4.75 magnesium gluconate hydrate in 100 ml of water was added dropwise at 25 ± 5 °C. The suspension was stirred for 2 hours at 20- 25°C.

The product was filtered and washed with 5 ml of water, dried at 35°C to obtain 5.9 g of magnesium esomeprazole.

5 Example 25

Preparation of physical mixtures of zinc esomeprazole

The following physical zinc esomeprazole mixtures with excipients were prepared mixed in a mortar (weight / weight):

Ingredient	Example 25.i.	Example 25.ii.	Example 25.iii.	Example 25.iv.	Example 25.v.	Example 25.vi.
Zinc esomeprazole	50%	9%	9%	9%	9%	20%
Urea	50%					
Colloidal anhydrous silica		91%				
Mannitol			91%			
Macrogol 6000				91%		
Sucrose					91%	
Povidone						80%

Example 26

Preparation of physical mixtures of zinc esomeprazole

- 5 The following mixtures of zinc esomeprazole and excipients were prepared (as 5 to 50 %) dispersion in ethanol (conc. 96%) and spray-dried on mini spray dryer Büchi 190 at the inlet temperature of 70 to 100 °C.
- 10 Mixtures refer to the composition of the dry part of the mixture (weight / weight).

Ingredient	Example 26.i.	Example 26.ii.	Example 26.iii.	Example 26.iv.	Example 26.v.	Example 26.vi.
Zinc esomeprazole	100%	50%	33%	9%	9%	80%
Urea		50%				
Colloidal anhydrous silica			67%			
Mannitol				91%		
Sucrose					91%	
Poloxamer 188						20%

Ingredient	Example 26.vii.	Example 26.viii.	Example 26.ix.
Zinc esomep- razole	67%	67%	80%
Calcium sul- phate	33%		
Calcium phosphate		33%	
Povidone			20%

Dissolution in phosphate buffer of initial zinc esomeprazole, spray-dried zinc esomeprazole according to example 26.i. and the physical mixture of zinc esomeprazole and povidone according to example 26.ix. are compared in Figure 4.

Example 27

Preparation of pellets comprising pharmaceutically acceptable salt of esomeprazole

5

The following pharmaceutically acceptable salts of esomeprazole were used for preparation of pellets:

- a.) magnesium esomeprazole dihydrate (amorphous)
- 10 b.) magnesium esomeprazole dihydrate (degree of crystallinity 65 %)
- c.) magnesium esomeprazole trihydrate
- d.) zinc esomeprazole
- e.) arginine esomeprazole

15

Magnesium esomeprazole dihydrate according to b.) with defined degree of crystallinity (i.e. 65 %) was obtained by mixing of amorphous magnesium esomeprazole dihydrate and magnesium esomeprazole dihydrate with degree of crystallinity of 100 %
20 (Form B according to Example 5 of EP-B-0 984 957).

Neutral pellets (microcrystalline cellulose or sugar spheres) were coated with pharmaceutically acceptable salt of esomeprazole in different manners:

25

- Example 27.i., 27.ii. and 27.vi. - suspension layering
- Example 27.iii. - powder layering
- Example 27.iv. - extrusion/spheronization
- Example 27.v. - rotor pelletization

30

Ingredient	Example 27.i.	Example 27.ii.	Example 27.iii.	Example 27.iv.	Example 27.v.
Neutral spheres (microcrystalline cellulose based)	41%				
Neutral spheres (sugar based)		57%	47%		
Esomeprazole salt (a. - e.)	32%	35%	28%	29%	28%
Hypromellose	5%		7%		
Magnesium carbon- ate	21%		11%		10%
Povidone		7%			
Sodium lauryl sulphate	1%	1%			1%
Meglumine			6%		
Colloidal anhy- drous silica			1%		
Methylcellulose				4%	
Zinc hydroxyde carbonate				14%	
Mannitol				14%	31%
Corn starch				8%	
Hyprollose, low- substituted				11%	
Hyprollose					5%
Microcrystalline cellulose				20%	25%

- 72 -

Ingredient	Example 27.vi.
Neutral spheres (microcrystalline cellulose based)	
Neutral spheres (sugar based)	54,1%
Esomeprazole salt (a. - e.)	33,1 %
Hypromellose	
Magnesium carbon- ate	
Povidone	11,4 %
Sodium lauryl sulphate	1,4 %
Meglumine	
Colloidal anhy- drous silica	
Methylcellulose	
Zinc hydroxyde carbonate	
Mannitol	
Corn starch	
Hyprollose, low- substituted	
Hyprollose	
Microcrystalline cellulose	

Example 28

Coating of pellets comprising pharmaceutically acceptable salt of esomeprazole with separating layer

5

Pellets, obtained according to Example 27 were coated with separating layer. The following compositions of the separating layer were used:

Ingredient	Example 28.i.	Example 28.ii.	Example 28.iii.	Example 28.iv.	Example 28.v.	Example 28.vi.
Pellets	80%	90%	89%	88%	90%	92%
Hypromellose	9%		9%	7%		
Povidone						8%
Talc	8%			3%	4%	
Dibasic sodium phosphate	1%					
Magnesium stearate	2%					
Methylcellulose		4%			6%	
Zinc hydroxide carbonate		6%				
Magnesium carbonate			2%			
Magnesium hydroxide				2%		

10

- 74 -

Ingredient	Example 28.i.
Pellets	94,4 %
Hypromellose	
Povidone	
Talc	
Dibasic sodium phosphate	
Magnesium ste- arate	
Methylcellulose	5,6 %
Zinc hydroxide carbonate	
Magnesium car- bonate	
Magnesium hy- droxyde	

Example 29

Coating of pellets comprising pharmaceutically acceptable salt of esomeprazole with enteric layer

5

Pellets, obtained according to Example 28 were coated with enteric layer. The following compositions of the separating layer were used:

Ingredient	Example 29.i.	Example 29.ii.	Example 29.iii.	Example 29.iv.
Pellets	62%	65%	63%	60%
Methacrylic acid ethyl acrylate copolymer	31%	29%	28%	31%
Triethyl citrate	3%			
Glyceryl monostearate	2%			
Polysorbate 80	1%		1%	1%
Propyleneglycol		4%		3%
Glyceryl monostearate		2%		1%
Macrogol 6000			2%	
Talc			3%	
Titanium dioxide			3%	
Ethyl acrylate methyl methacrylate copolymer				3%

- 76 -

Ingredient	Example 29.v.	Example 29.vi.
Pellets	66,2 %	73,0 %
Methacrylic acid ethyl ac- rylate copoly- mer	21,8 %	17,5 %
Triethyl cit- rate		
Glyceryl monostearate		
Polysorbate 80	1,0 %	0,8 %
Propyleneglycol		
Glyceryl monostearate		
Macrogol 6000	2,2 %	1,7 %
Talc	6,6 %	5,3 %
Titanium diox- ide	2,2 %	1,7 %
Ethyl acrylate methyl methac- rylate copoly- mer		

Example 30

Coating of pellets comprising pharmaceutically acceptable salt of esomeprazole with overcoating layer

5

Pellets, obtained according to Example 29 were coated with enteric layer. The following compositions of the overcoating layer were used:

Ingredient	Example 30.i.	Example 30.ii.	Example 30.iii.
Pellets	92%	89%	92%
Hyprollose	4.5%		3.5%
Microcrystalline cellulose	2.4%	7%	3.5%
Polyethyleneglycol 6000	0.3%		1%
Titanium dioxide	0.8%		
Methylcellulose		4%	

10

Example 31

Preparation of tablets comprising pharmaceutically acceptable
salt of esomeprazole

5

Pellets, obtained according to Example 30 were further ta-
bleted. The following compositions of pellets and excipients
were used:

Ingredient	Example 31.i.	Example 31.ii.
Pellets	29.8%	31%
Microcrystalline cellulose	70%	56%
Sodium stearyl fu- marate	0.2%	
Crospovidone		9%
Polyethyleneglycol 6000		3%
Magnesium stearate		1%

10

- 79 -

Example 32

Preparation of enteric coated tablets comprising pharmaceutically acceptable salt of esomeprazole

5

Pellets, obtained according to Example 27 were tableted and further coated with enteric coating. The compositions of pellets and excipients were used:

Ingredient	Example 32.i.	Example 32.ii.	Example 32.iii.	Example 32.iv.
Methacrylic acid ethyl acrylate copolymer	82%	83%	74%	78%
Triethyl citrate	8%			
Glyceryl monostearate	5%			
Polysorbate 80	3%		2%	2%
Propyleneglycol		11%		8%
Glyceryl monostearate		6%		2%
Macrogol			8%	
Talc			8%	
Titanium dioxide			8%	
Ethyl acrylate methyl methacrylate copolymer				8%

Example 33

Preparation of pharmaceutically acceptable salt of esomeprazole tablets comprising overcoating layer or enteric coating
5 and overcoating layer

Tablets, obtained according to Example 31 and 32 were further coated with overcoating layer. The following composition of excipients was used:

10

Ingredient	Example 33.i
Hypromellose	90%
Polyethyleneglycol 6000	5%
Titanium dioxide	5%

Example 34

Preparation of tablets comprising pharmaceutically acceptable salt of esomeprazole by direct compression and enteric coating

5

The pharmaceutically acceptable salt of esomeprazole as described in Example 27. (a. - e.) were mixed in a high shear mixer (optionally in biconic blender), directly compressed and coated according to example 32.

10

Ingredient	Example 34.i.	Example 34.ii.	Example 34.iii.	Example 34.iv.	Example 34.v.	Example 34.vi
Esomeprazole salt (a. - e.)	20%	20%	20%	20%	20%	20%
Microcrystalline cellulose	66%			74%		
Lactose monohydrate		66%			74%	
Cellactose			66%			74%
Crospovidone	10%	10%	10%			
Croscarmellose sodium				2%	2%	2%
Colloidal anhydrous silica	2%	2%	2%	2%	2%	2%
Magnesium stearate	2%	2%	2%			
Hydrogenated castor oil				2%	2%	2%

Example 35

Composition of tablets comprising magnesium salt of esomeprazole

5

Ingredient	Example 35.i.
Core material	
Esomeprazole Mg	38,7 %
Cellactose	48,9 %
Microcrystalline cellulose	7,4 %
Croscarmellose sodium	3,0 %
Magnesium stearate	2,0 %

Separating layer	
Core material	88,7 %
Methylcellulose	8,6 %
Titanium dioxide	0,3 %
Iron Oxide Yellow	0,1
Propyleneglycol	2,3 %

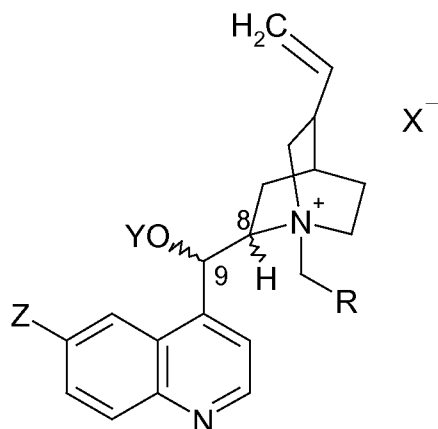
Enteric coating	
Tablets with separating layer	92,8 %
Methacrylic acid ethyl acrylate copolymer	4,9 %
Macrogol	0,5 %
Talc	1,8 %

- 83 -

Claims

1. A process for the preparation of substantially optically pure omeprazole, or a pharmaceutically acceptable salt or solvate thereof, comprising the steps of:
 - (a) contacting omeprazole or a salt thereof with a resolving agent selected from a chiral amine or a chiral quaternary ammonium salt in a solvent to give a diastereomeric pair of omeprazole ammonium salts;
 - (b) separating the diastereomeric pair of omeprazole ammonium salts to give a substantially optically pure omeprazole ammonium salt;
 - (c) converting the omeprazole ammonium salt to obtain substantially optically pure omeprazole or a pharmaceutically acceptable salt or solvate thereof; and
 - (d) optionally transforming the substantially optically pure omeprazole into a pharmaceutically acceptable salt or solvate thereof.
2. The process according to claim 1, wherein the resolving agent is selected from the group consisting of (-)-brucine, (+)- α -methylbenzylamine, (-)-ephedrine, N,N-dimethylephedrine, bis-(1-phenylethyl)amine, cinchona bases, and quaternary salts thereof.
3. The process according to claim 1, wherein the resolving agent is a quaternary cinchona salt of formula **(I)**:

- 84 -



(I),

wherein

Z is hydrogen or methoxy;

Y is hydrogen, benzyl or allyl;

R is hydrogen or phenyl;

X is iodine, bromine, chlorine or hydroxy;

and wherein the configuration at C(8) and C(9) is independently (R) or (S).

4. The process according to claim 3, wherein the resolving agent is a quaternary salt of a cinchona base selected from the group consisting of (-)-quinine, (+)-quinidine, (+)-cinchonine and (-)-cinchonidine.
5. The process according to any one of claims 1 to 4, wherein the solvent of step (a) comprises at least one solvent which is selected from the group consisting of (C₁-C₅) alcohols, (C₃-C₆) ketones, acetonitrile, dimethylformamide, aromatic (C₆-C₉) hydrocarbons, tetrahydrofuran, aliphatic (C₁-C₄) esters, halogenated aliphatic (C₁-C₉) hydrocarbons and optionally comprises up to 50 vol-% water.

- 85 -

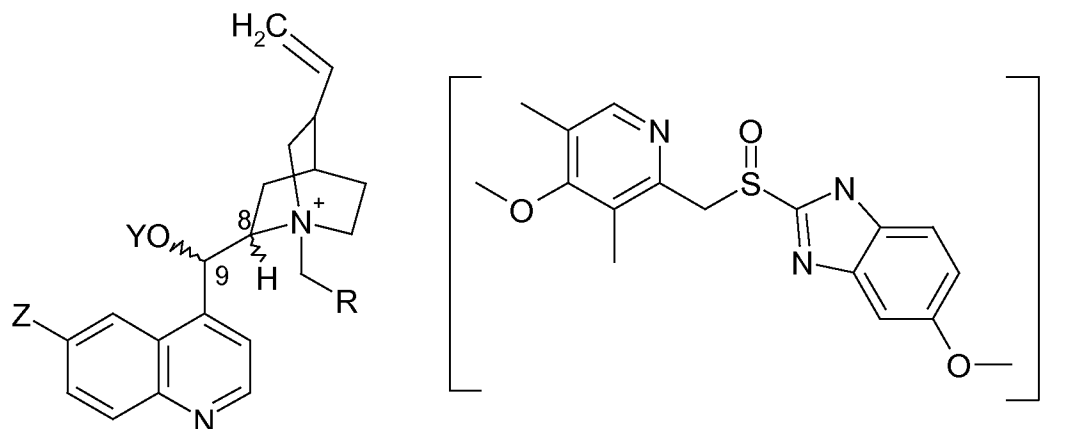
6. The process according to claim 5, wherein the solvent of step (a) comprises no more than 35 vol-%, preferably no more than 20 vol-%, most preferably no more than 15 vol-% water.
7. The process according to any one of claims 1 to 6, wherein the resolving agent is used in an amount of at least 0.7 equivalents, preferably at least 0.9 equivalents, most preferably at least 1 equivalent, based on the molar amount of omeprazole.
8. The process according to any of claims 1 to 7, wherein between steps (a) and (b) the diastereomeric pair of omeprazole ammonium salts is recovered preferably by evaporation of solvent(s) under reduced pressure.
9. The process according to any of claims 1 to 8, wherein step (b) comprises crystallizing omeprazole ammonium salt from a solvent for crystallization.
10. The process according to claim 9 wherein the solvent for crystallization comprises at least one solvent selected from the group consisting of (C₁-C₅) alcohols, (C₃-C₆) ketones, acetonitrile, dimethylformamide, aromatic (C₆-C₉) hydrocarbons, tetrahydrofuran, aliphatic (C₁-C₄) esters, halogenated aliphatic (C₁-C₉) hydrocarbons.
11. The process according to any of claims 1 to 10, wherein step (c) comprises contacting the omeprazole ammonium salt with at least one compound selected from the group consisting of an acid, an acidic salt and an acidic ion exchanger.
12. The process according to any of claims 1 to 11 wherein the conversion of step (c) is carried out in a solvent system

- 86 -

comprising water and at least one water-immiscible solvent.

13. The process according to claim 12, wherein the water-immiscible solvent is selected from the group consisting of (C₆-C₉) aromatic hydrocarbons, aliphatic (C₂-C₈) ethers, aliphatic (C₁-C₄) esters, halogenated aromatic and aliphatic (C₁-C₉) hydrocarbons.
14. The process according to any one of claims 1 to 13 wherein the pharmaceutically acceptable solvate is (S)-omeprazole magnesium dihydrate form A.
15. Process for preparing a pharmaceutical composition comprising substantially optically pure omeprazole, or a pharmaceutically acceptable salt or solvate thereof, in combination with at least one pharmaceutically acceptable carrier, which includes the step of preparing the substantially optically pure omeprazole or the pharmaceutically acceptable salt or solvate thereof according to the process of any one of claims 1 to 14.
16. An omeprazole ammonium salt, wherein the ammonium moiety is derived from a chiral amine selected from the group consisting of (-)-brucine, (+)- α -methylbenzylamine, (-)-ephedrine, N,N-dimethylephedrine and bis-(1-phenylethyl)-amine.
17. An omeprazole ammonium salt having the formula **(II)**:

- 87 -



(II),

wherein:

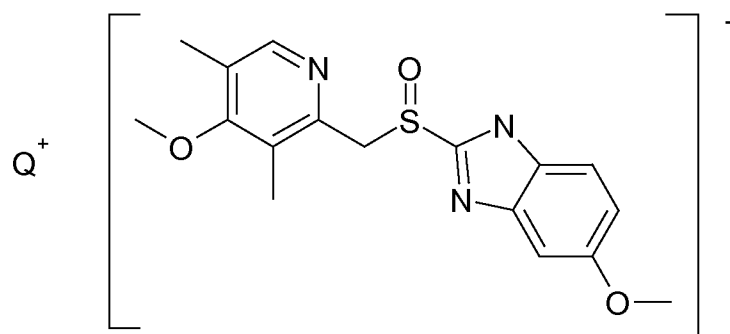
the configuration at C(8), C(9) and the sulfur atom is independently (R) or (S);

Z is hydrogen or methoxy;

Y is benzyl or allyl; and

R is hydrogen or phenyl.

18. An omeprazole ammonium salt having the formula (III):



(III),

wherein the configuration at the sulfur atom is independently (R) or (S) and wherein Q⁺ is selected from the group consisting of:

- 89 -

19. A process for preparing enantiomerically enriched omeprazole comprising:

a.) preparation of racemic or enantiomerically enriched omeprazole

b.) treatment of racemic or enantiomerically enriched omeprazole according to a.) by enzyme wherein enantiomerically selective conversion takes place on an atom other than sulfur

c.) separation of the obtained mixture comprising enantiomerically enriched omeprazole and derivatives, wherein percentage of enantiomerically enriched omeprazole is different than the percentage of enantiomerically enriched omeprazole in step a.)

d.) optionally further purification of enantiomerically enriched omeprazole, preparation of pharmaceutically acceptable salt of enantiomerically enriched omeprazole and optionally preparation of pharmaceutical formulation.

20. The process according to claim 19, wherein the enzyme is selected from cytochrome P450 enzyme.

21. The process according to claim 20, wherein the cytochrome P450 enzyme is CYP2C19.

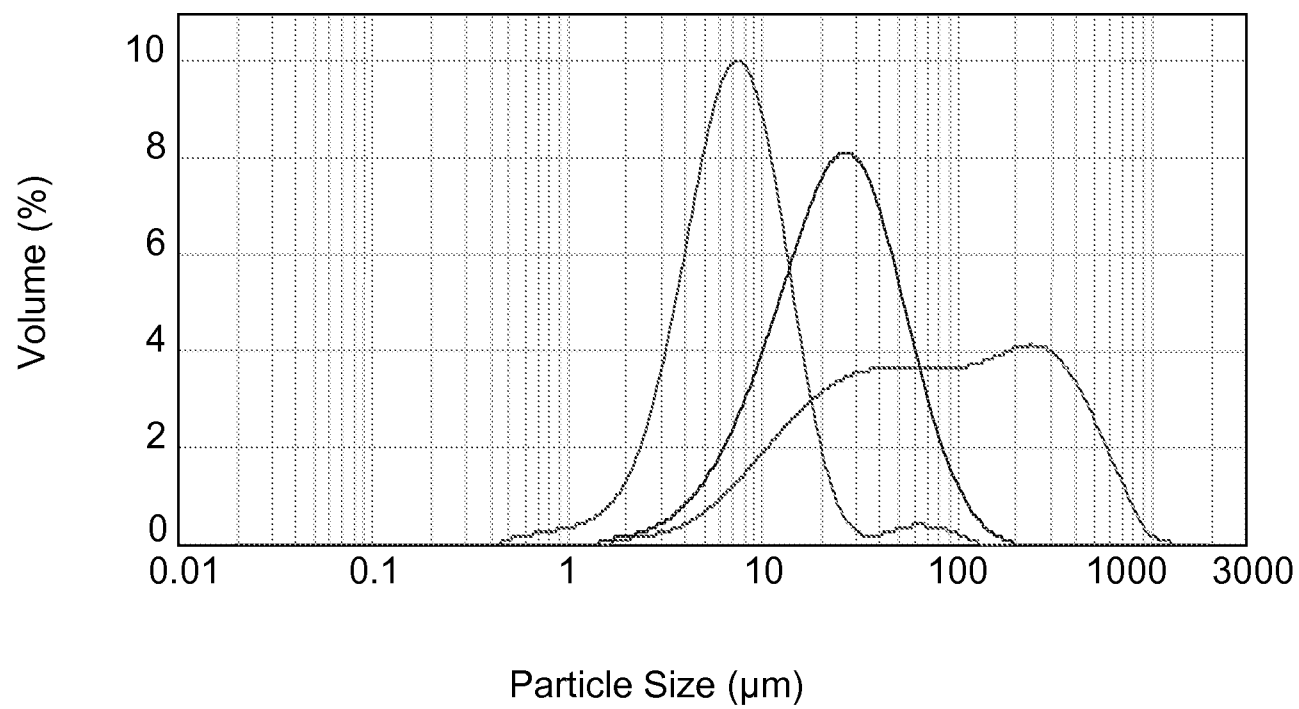
22. The process according to any one of claim 19 to 21, wherein the obtained mixture comprises 5-hydroxy and/or 5-O-desmethyl derivatives of omeprazole.

23. The process according to any one of claims 19 to 22, wherein the separation of enantiomerically enriched omeprazole is performed chromatographic column.

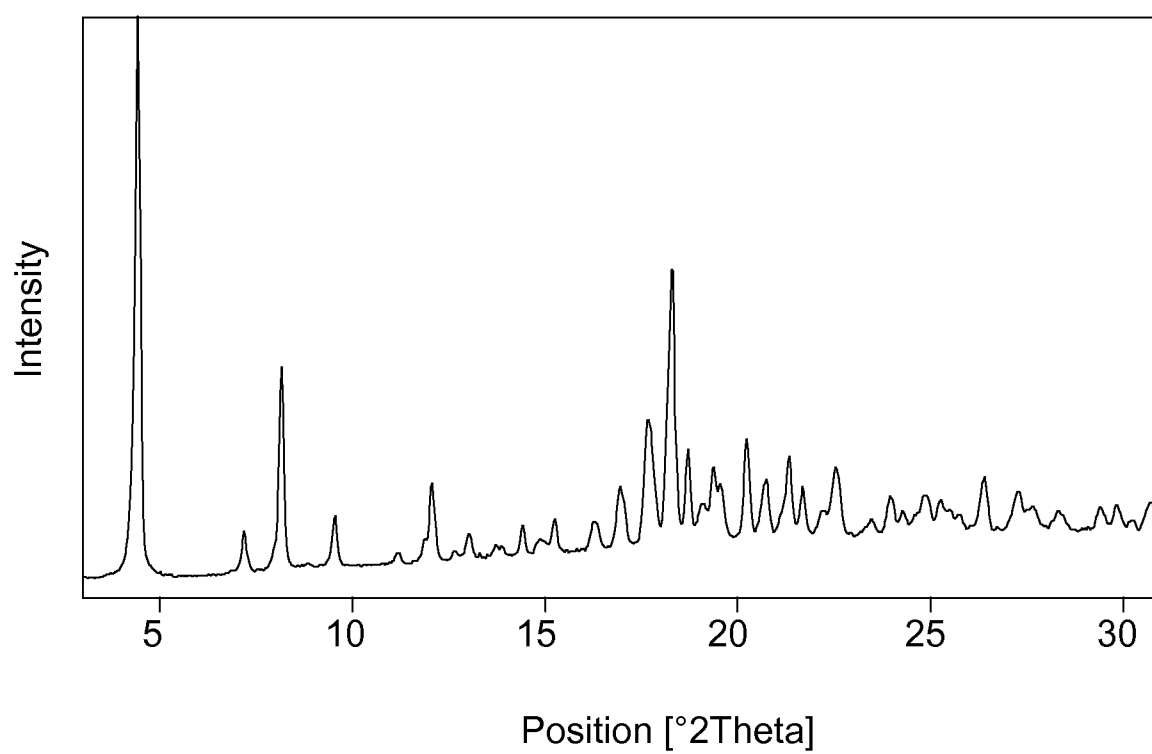
- 90 -

24. The process according to Claim 23, wherein the chromatographic column comprises dimethyl N-3,5-dinitrobenzoyl-L-amino-2,2-dimethyl-4-pentenyl phosphonate covalently bound to mercaptopropyl silica.
25. The process according to Claim 24, wherein the R-(+)-omeprazole is the more retained component and will elute after S-(-)-omeprazole.
26. The process according to any one of claims 19 to 25, wherein the pharmaceutically acceptable salt of esomeprazole is selected from the group consisting of esomeprazole magnesium, esomeprazole arginine, esomeprazole zinc, and solvates thereof.
27. The process according to claim 26, wherein solvates are from the group of monohydrate, dihydrate and trihydrate.
28. The process according to claim 27, wherein solvate is dihydrate.
29. The process according to any one of claims 26 to 28, wherein the degree of crystallinity is in the range of 50 % to 100 %.
30. The process according to Claim 29, wherein the degree of crystallinity is in the range of 60 % to 90 %.
31. The process according to any one of claims 19 to 30, wherein the pharmaceutical formulation is prepared from physical mixture comprising zinc esomeprazole and povidone.

- 1 / 4 -

Figure 1

- 2 / 4 -

Figure 2

- 3 / 4 -

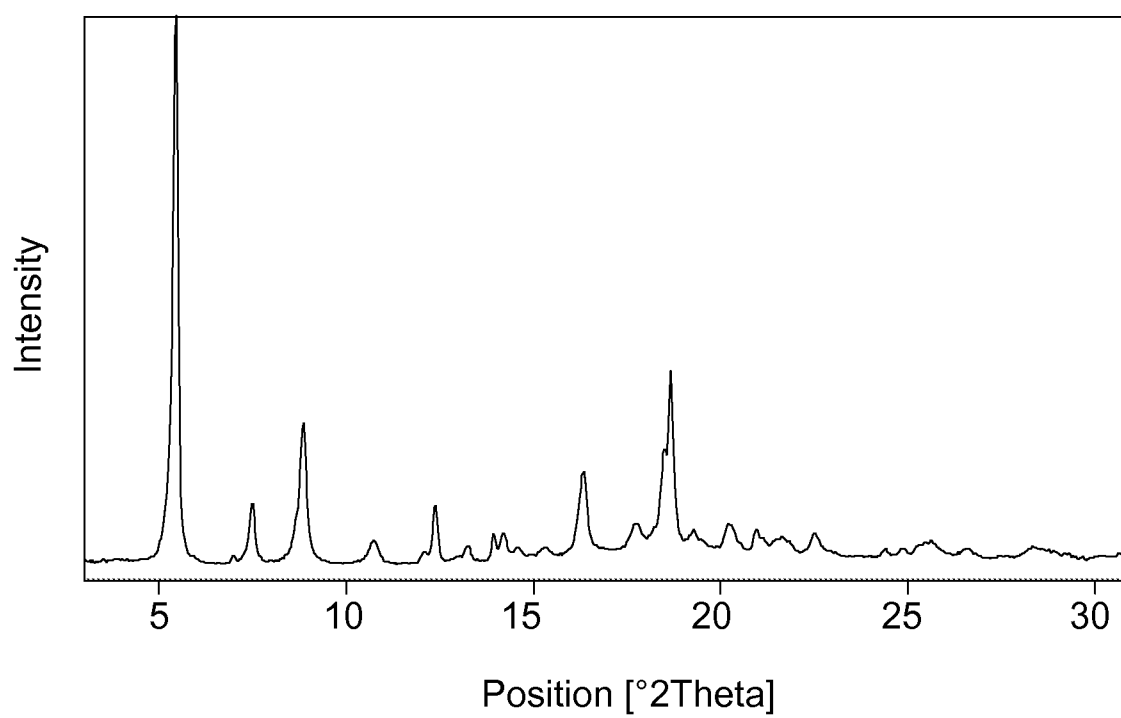
Figure 3

Figure 4

