

CLAIMS

1. A pharmaceutical composition comprising rifaximin or one of the pharmaceutically acceptable salts thereof and one or more aromatic amino acid or a heterocyclic amino acid(s), wherein the molar ratio between the amino acid(s) and rifaximin is from 1:1 to 10:1, together with one or more pharmaceutically acceptable excipients.
2. The pharmaceutical composition according to claim 1, wherein the molar ratio between the amino acid(s) and rifaximin is from 1:1 to 5:1.
3. The pharmaceutical composition according to claim 1, wherein the rifaximin is present in the pharmaceutical composition as a crystalline, polymorphous, amorphous, hydrate, or solvate form or as a mixture thereof.
4. The pharmaceutical composition according to claim 3, wherein the crystalline form of rifaximin is selected from
- i) a form having monoclinic space group $P2_1$ and cell parameters in the ranges: a: 13.7(1)-13.8(1) Å; b: 19.7(1)-19.9(1) Å; c: 16.4(6)-16.6(6) Å; β : 92.1(1)-91.9(1) deg.,
 - ii) the form of i) comprising 3 or 4.5 water molecules for each rifaximin molecule,
 - iii) a form having monoclinic space group $P2_1$ and cell parameters in the ranges: a: 14.2(1)-14.5(1) Å; b: 19.7(1)-20.1(1) Å; c: 16.1(1)-16.2(1) Å; β : 108.7(1)-111.4(1) deg.
 - iv) the form of iii) comprising zero or 0.5 or 1.5 water molecules for each rifaximin molecule, or
 - v) a form of rifaximin α , β , γ , or δ .
5. The pharmaceutical composition according to claim 1, wherein rifaximin is in a dosage from 20 mg to 1200 mg.
6. The pharmaceutical composition according to claim 1, wherein the one or more

amino acid(s) further comprise one or more amino acid(s) is/are selected from the group consisting of aliphatic amino acids, basic amino acids, branched amino acids, cyclic amino acids, acidic amino acids, hydroxyl or sulfur containing amino acids, amide amino acids and mixtures thereof.

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7. The pharmaceutical composition according to claim 1, wherein the one or more amino acid(s) is/are selected from histidine, tryptophan, phenyl alanine, tyrosine, and proline.

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8. The pharmaceutical composition according to claim 6, wherein the one or more further comprised amino acid(s) is/are branched amino acids.

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9. The pharmaceutical composition according to claim 1, wherein the one or more further comprised amino acid(s) are selected from valine, leucine and isoleucine; and wherein the molar ratio between the amino acids and rifaximin is 10:1.

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10. The pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable excipients include one or more of: diluting agents, binding agents, disintegrating agents, lubricating agents, release-controlling polymers and bioadhesive polymers.

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11. The pharmaceutical composition of claim 10, wherein the diluting agent is at least one selected from the group consisting of: cellulose, microcrystalline cellulose, calcium phosphate, starch, kaolin, dehydrated calcium sulphate, calcium carbonate, lactose, saccharose, glucose, sorbitol and mannitol.

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12. The pharmaceutical composition of claim 10, wherein the binding agent is at least one selected from the group consisting of: cellulose, cellulose derivatives, carboxy methyl cellulose, microcrystalline cellulose, hydroxy propyl cellulose, hydroxy ethyl cellulose, hydroxy propyl-methyl cellulose, starches, potato starch, maize starch, partially gelatinized starch, gums, synthetic gum, natural gums, polyvinyl pyrrolidone, polyethylene glycol, gelatin, polyols, propylene glycol, alginates and sugars.

13. The pharmaceutical composition of claim 10, wherein the disintegrating agent is at least one selected from the group consisting of: sodium carboxy methyl cellulose, cross-linked sodium carboxy methyl cellulose, polyvinyl pyrrolidone, cross-linked polyvinyl pyrrolidone, starch, pre-gelatinized starch and silica.
14. The pharmaceutical composition of claim 10, wherein the lubricating agent is at least one selected from the group consisting of: silica, magnesium stearate, calcium stearate, sodium stearyl fumarate, hydrogenated vegetable oils, mineral oils, polyethylene glycols, sodium lauryl sulphate, glycerides, sodium benzoate, glyceryl dibehenate and glycerol stearate.
15. The pharmaceutical composition of claim 10, wherein the release-controlling polymer is at least one selected from the group consisting of: copolymers of acrylic acid, copolymers of methacrylic acid with an acrylic or methacrylic ester, polyvinyl acetate phthalate, hydroxy propyl methyl cellulose phthalate, cellulose acetate phthalate, Kollicoat®, Eudragit®, Aquateric®, Aqoat®; natural polymers and ethyl cellulose.
16. The pharmaceutical composition of claim 10, wherein the bioadhesive polymer is at least one selected from the group consisting of: pectins, zeins, casein, gelatin, albumin, collagen, kitosan, cellulose, dextran, polysaccharides from tamarind seeds, xanthan gum, arabic gum, hyaluronic acid, alginic acid, sodium alginate, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl pyrrolidone, polysiloxanes, polyurethanes, polystyrenes, polymers of acrylic acid and methacrylic esters, copolymers of methacrylic acid-ethyl acrylate, polylactides, barbituric polyacids, polyanhydrides, polyorthoesters, methyl cellulose, ethyl cellulose, hydroxy propyl cellulose, hydroxy butyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxy methyl cellulose, cellulose triacetate, cellulose sulfate sodium salt, polymethyl methacrylate, poly isobutyl acrylate, poly octadecyl acrylate, polypropylene, polyethylene glycol, polyethylene oxide, polyethylene terephthalate, polyvinyl acetate, polyvinyl chloride,

polystyrene, polyvinyl phenol, carboxylic acids, sulphonic acids, phosphonic acids, and neutral and positively charged amines, amides and imines.

17. The pharmaceutical composition according to claim 1, wherein the composition is in the form of a powder, paste, tablet, capsule, ovules cream, foam, suspension, solution, aerosol, granulates, ointment or suppository suitable for human or animal administration.

18. The pharmaceutical composition according to claim 17, wherein the composition is in a form for oral or vaginal or topical administration.

19. The pharmaceutical composition of claim 18, wherein the composition includes rifaximin in an amount from 20 to 1200 mg.

20. The pharmaceutical composition of claim 19, wherein the composition includes rifaximin in an amount from 100 to 600 mg.

21. The pharmaceutical composition according to claim 1, wherein the one or more pharmaceutically acceptable excipients are selected from the group consisting of edulcorating agents, coloring agents, anti-oxidizing agents, buffering agents and flavoring agents.

22. The pharmaceutical composition according to claim 21, wherein the edulcorating agent is at least one selected from the group consisting of potassium acesulfame, sorbitol, mannitol, isomalt, maltitol, lactitol, xylitol, aspartame, cyclamic acid, cyclamate salts, lactose, sucralose, saccharine and saccharine salts.

23. A process for the production of rifaximin crystals, said process comprising:

a) dissolving rifaximin and one or more aromatic or heterocyclic amino acids, wherein the amino acids and rifaximin are in a molar ratio from 1:1 to 10:1 in a solution consisting of ethanol and water in a volumetric ratio from 1:1 to 1:10 (v/v);

b) evaporating the solution obtained in step a) to obtain rifaximin crystals.

24. The process according to claim 23, wherein the evaporation of the solution takes place at temperatures from room temperature to 40°C.
- 5 25. The process according to claim 23, wherein the evaporation of the solution takes place in a time period from 1 to 10 days.
26. The process according to claim 23, wherein the resulting crystals are characterized by monoclinic space group $P2_1$ and cell parameters comprised in the
10 ranges:
a: 13.7(1)-13.8(1) Å; b: 19.7(1)-19.9 (1) Å; c: 16.4(6)-16.6(6) Å; β : 92.1(1)-
91.9(1) deg.
27. The process according to claim 23, wherein evaporating the solution is
15 performed in the presence of dehydrating agents.
28. The process according to claim 27, wherein the evaporation of the solution takes place at temperatures from room temperature to 40°C.
29. The process according to claim 23, wherein the evaporation of the solution takes place in a time period from 1 to 10 days.
30. The process according to claim 27, wherein the resulting crystals have monoclinic space group $P2_1$ and cell parameters comprised in the ranges: a: 14.2(1)-
25 14.5(1) Å; b: 19.7(1)-20.1(1) Å; c: 16.1(1)-16.2(1) Å; β : 108.7(1)-111.4(1) deg.
31. A composition comprising one or more aromatic or heterocyclic amino acids and rifaximin wherein the molar ratio between the amino acids and rifaximin is from 1:1 to
30 10:1.
32. The composition according to claim 31, in the form of an aqueous solution and wherein the rifaximin concentration is from 4.5 µg/ml to 60 µg/ml at room temperature.

- 5 33. The composition according to claim 31, wherein said composition is in the form of a conglomerate.
34. The composition according to claim 32, wherein the aqueous solution further comprises one or more organic solvents in an amount from 1% to 25% v/v.

CLAIMS

1. Pharmaceutical composition comprising rifaximin or one of the pharmaceutically acceptable salts thereof and one or more amino acid(s), wherein the molar ratio between the amino acid(s) and rifaximin is comprised between 1:1 and 10:1, preferably between 1:1 and 5:1, together with pharmaceutically acceptable excipients.

2. The pharmaceutical composition according to claim 1, wherein the rifaximin is in the crystalline, polymorphous or amorphous form, in the form of a hydrate or solvate and/or in a mixture thereof.

3. The pharmaceutical composition according to claim 2, wherein the crystalline form of rifaximin is selected from

i) crystals having monoclinic space group $P2_1$ and cell parameters comprised in the ranges:

a: 13.7(1)-13.8(1) Å; b: 19.7(1)-19.9 (1) Å; c: 16.4(6)-16.6(6) Å; β : 92.1(1)-91.9(1) deg.,

ii) crystals having the features of i) and having 3 or 4.5 water molecules for each rifaximin molecule,

iii) crystals having monoclinic space group $P2_1$ and cell parameters comprised in the ranges:

a: 14.2(1)-14.5(1) Å; b: 19.7(1)-20.1(1) Å; c: 16.1(1)-16.2(1) Å; β : 108.7(1)-111.4(1) deg.

iv) crystals having the features of iii) and having zero or 0.5 or 1.5 water molecules for each rifaximin molecule, or

v) rifaximin α , β , γ , δ .

4. The pharmaceutical composition according to one of claims 1 to 3, wherein rifaximin is in a dosage from 20 mg to 1200 mg.
5. The pharmaceutical composition according to one of claims 1 to 4, wherein the amino acid(s) is/are selected from aliphatic amino acids, aromatic amino acids, basic amino acids, heterocyclic amino acids, branched amino acids, cyclic amino acids, acid amino acids, amide amino acids or mixtures thereof.
6. The pharmaceutical composition according to one of claims 1 to 4, wherein the composition comprises at least one aromatic or heterocyclic amino acid.
7. The pharmaceutical composition according to one of claims 1 to 5, wherein the amino acid(s) is/are selected from serine, histidine, tryptophan, valine, leucine or isoleucine.
8. The pharmaceutical composition according to one of claims 1 to 4, wherein the amino acid(s) is/are selected from branched chain amino acids.
9. The pharmaceutical composition according to one of claims 1 to 3, comprising rifaximin and valine, leucine or isoleucine in a molar ratio of 10:1 with respect to rifaximin.
10. The pharmaceutical composition according to one of claims 1 to 9, wherein the pharmaceutically acceptable ingredients include diluting agents, binding agents, disintegrating agents, lubricating agents, release-controlling polymers or bioadhesive polymers.
11. The pharmaceutical composition according to one of claims 1 to 10, wherein the composition is in the form of a tablet, capsule, cream, suspension, solution, granulates, ointment or suppository suitable for human or animal administration.

12. The pharmaceutical composition according to one of claims 1 to 11, wherein the composition is in a form for oral administration.

13. A pharmaceutical composition according to one of claims 1 to 12 for use in the treatment or prevention of bowel infections, diarrhoea, irritable bowel syndrome, bacterial growth in small intestine, Crohn's disease, hepatic insufficiency, hepatic encephalopathy, enteritis, fibromyalgia.

14. A pharmaceutical composition according to one of claims 1 to 4, wherein at least one amino acid is a branched chain amino acid for use in the treatment of hepatic encephalopathy.

15. A process for the preparation of a pharmaceutical composition according to one of claims 1 to 12 comprising the steps:

- mixing rifaximin and amino acids;
- adding the excipients and mixing the final mixture in a V mixer for a time between 10 and 30 minutes and
- granulating in a roller compactor.

16. The process according to claim 15 wherein rifaximin and amino acid are mixed and then added to excipients for the obtainment of the composition as tablets, granulates, ointments, creams, suppositories, solution.

17. Use of an amino acid for obtaining a pharmaceutical composition having a rifaximin concentration from 4.5 µg/ml to 60 µg/ml.

18. Rifaximin crystals characterized in that they are obtained by means of a process comprising:

- a) dissolution of the compositions of rifaximin and amino acids, wherein amino acids and rifaximin are in a molar ratio comprised between 1:1 and 10:1 according to claim 1, in solutions formed by ethanol/water, in a volumetric ratio comprised between 1:1 and 1:10 (v/v);

b) evaporation of the solution obtained in step a) at temperatures comprised between room temperature and 40°C, in a time period comprised between 1 and 10 days;

wherein the resulting crystals have monoclinic space group $P2_1$ and cell parameters comprised in the ranges:

a: 13.7(1)-13.8(1) Å; b: 19.7(1)-19.9 (1) Å; c: 16.4(6)-16.6(6) Å; β : 92.1(1)-91.9(1) deg.

19. Rifaximin crystals according to claim 18, characterized in that they have

- i) 3 water molecules for each rifaximin molecule, or
- ii) 4.5 water molecules for each rifaximin molecule.

20. Rifaximin crystals characterized in that they are obtained by means of a dehydration process of the crystals obtained according to claim 18, in the presence of dehydrating agents, wherein the resulting crystals have monoclinic space group $P2_1$ and cell parameters comprised in the ranges:

a: 14.2(1)-14.5(1) Å; b: 19.7(1)-20.1(1) Å; c: 16.1(1)-16.2(1) Å; β : 108.7(1)-111.4(1) deg.

21. Rifaximin crystals according to claim 20, characterized in that they have

- i) zero water molecules for each rifaximin molecule, or
- ii) 0.5 water molecules for each rifaximin molecule, or
- iii) 1.5 water molecules for each rifaximin molecule.

22. Process for the production of rifaximin crystals, characterized in that it comprises:

a) dissolution of the compositions of rifaximin and amino acids, wherein amino acids and rifaximin are in a molar ratio comprised between 1:1

and 10:1 according to claim 1, in solutions formed by ethanol/water, in a volumetric ratio comprised between 1:1 and 1:10 (v/v);

b) evaporation of the solution obtained in step a) at temperatures comprised between room temperature and 40°C, in a time period comprised between 1 and 10 days;

wherein the resulting crystals are characterized by monoclinic space group $P2_1$ and cell parameters comprised in the ranges:

a: 13.7(1)-13.8(1) Å; b: 19.7(1)-19.9 (1) Å; c: 16.4(6)-16.6(6) Å; β : 92.1(1)-91.9(1) deg.

23. Process for the production of rifaximin crystals, characterized in that it comprises:

a) dissolution of the compositions of rifaximin and amino acids, wherein amino acids and rifaximin are in a molar ratio comprised between 1:1 and 10:1 according to claim 1, in solutions formed by ethanol/water, in a volumetric ratio comprised between 1:1 and 1:10 (v/v);

b) evaporation of the solution obtained in step a) at temperatures comprised between room temperature and 40°C, in a time period comprised between 1 and 10 days, in the presence of dehydrating agents;

wherein the resulting crystals have monoclinic space group $P2_1$ and cell parameters comprised in the ranges:

a: 14.2(1)-14.5(1) Å ; b: 19.7(1)-20.1(1) Å; c: 16.1(1)-16.2(1) Å; β : 108.7(1)-111.4(1) deg.

24. Use of amino acids and rifaximin in a molar ratio comprised between 1:1 and 10:1 in order to obtain rifaximin crystals, characterized by monoclinic space group $P2_1$ and cell parameters comprised in the ranges:

a: 13.7(1)-13.8(1) Å; b: 19.7(1)-19.9 (1) Å; c: 16.4(6)-16.6(6) Å; β : 92.1(1)-91.9(1) deg.

25. Use of amino acids and rifaximin in a molar ratio comprised between 1:1 and 10:1 in order to obtain rifaximin crystals, characterized by monoclinic space group $P2_1$ and cell parameters comprised in the ranges:

a: 14.2(1)-14.5(1) Å ; b: 19.7(1)-20.1(1) Å; c: 16.1(1)-16.2(1) Å; β : 108.7(1)-111.4(1) deg.