SOLID PHARMACEUTICAL DOSAGE FORM COMPRISING AN HIV PROTEASE INHIBITOR SOLID DISPERSION

SUMMARY

In one aspect, there is provided a solid pharmaceutical dosage form comprising:

lopinavir and ritonavir formulated in solid dispersion;

a pharmaceutically acceptable water-soluble polymer having a Tg of at least 50°C, and

a pharmaceutically acceptable surfactant having an HLB value of from 4 to 10.

In another aspect, there is provided a solid pharmaceutical dosage form comprising:

lopinavir and ritonavir formulated in solid dispersion;

a pharmaceutically acceptable water-soluble polymer having a Tg of at least 50 °C, and

a combination of surfactants having an HLB value of from 4 to 10.

DETAILED DESCRIPTION

The present invention is directed to a solid pharmaceutical dosage form comprising at least one HIV protease inhibitor, and a process for preparing same.

The virus causing acquired immunodeficiency syndrome (AIDS) is known by different names, including T-lymphocyte virus III (HTLV-III) or lymphadenopathy-associated virus (LAV) or AIDS-related virus (ARV) or human immunodeficiency virus (HIV). Up until now, two distinct families have been identified, i. e., HIV-1 and HIV-2.

One of the critical pathways in a retroviral life cycle is the processing of polyprotein precursors by aspartic protease. For instance with the HIV virus the gag-pol protein is processed by HIV protease. The correct processing of the precursor polyproteins by the aspartic protease is required for the assembly of infectious virions, thus making the aspartic protease an attractive target for antiviral therapy. In particular for HIV treatment, the HIV protease is an attractive target.

A measure of the potential usefulness of an oral dosage form of a pharmaceutical agent is the bioavailability observed after oral administration of the dosage form. Various factors can affect the bioavailability of a drug when administered orally. These factors include aqueous solubility, drug absorption throughout the gastrointestinal tract, dosage strength and first pass effect. Aqueous solubility is one of the most important of these factors. Unfortunately, HIV protease inhibiting compounds typically are characterized by having poor aqueous solubility.

For a variety of reasons, such as patient compliance and taste masking, a solid dosage form is usually preferred over a liquid dosage form. In most instances however, oral solid dosage forms of a drug provide a lower bioavailability than oral solutions of the drug.

We claim:

1. A solid pharmaceutical dosage form which comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C.

2. The dosage form of claim 1 comprising a glassy solution or solid solution of said HIV protease inhibitor.

3. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant has an HLB value of from about 4 to about 10.

4. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant is a combination of at least one pharmaceutically acceptable surfactant having an HLB value of from about 4 to about10 and at least one further pharmaceutically acceptable surfactant.

5. The dosage form of Claim 1 wherein said pharmaceutically acceptable surfactant is a sorbitan fatty acid ester.

6. The dosage form of Claim 1 which comprises, relative to the weight of the dosage form, from about 5 to about 30 % by weight of said HIV protease inhibitor, from about 50 to about 85 % by weight of said water-soluble polymer, from about 2 to about 20 % by weight of said surfactant, and from about 0 to about 15 % by weight of additives.

7. The dosage form of claim 1, wherein said HIV protease inhibitor is selected from the group consisting of: 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir); (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir); N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-

pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);
N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);
5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;
1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4t-butylamide;
5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;
[1S-[1R-(R-),2S*])-N'-[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;
amprenavir (VX-478); DMP-323; DMP-450; AG1343 (nelfinavir);
atazanavir (BMS 232,632)
tipranavir
palinavir
TMC-114
RO033-4649
fosamprenavir (GW433908)
P-1946,
BMS 186,318; SC-55389a; BILA 1096 BS; U-140690,
or combinations thereof.

8. The dosage form of Claim 1 wherein said HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

9. The dosage form of Claim 8 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of ritonavir plasma concentration of at least about 9 μg.h/ml/100 mg.

10. The dosage form of Claim 1 wherein said HIV protease inhibitor is (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)-amino-3-hydroxy-5-[2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl]amino-1,6-diphenylhexane (lopinavir).

11. The dosage form of claim 10 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of lopinavir plasma concentration of at least about 20 μg.h/ml/100 mg.

12. The dosage form of claim 1 wherein said HIV protease inhibitor is a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydropyrimid-2-onyl)-3-methylbutanoyl] amino-1,6-diphenylhexane (lopinavir).

13. The dosage form of claim 12 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of ritonavir plasma concentration of at least 9 about μg.h/ml/100 mg and a dose-adjusted AUC of lopinavir plasma concentration of at least about 20 μg.h/ml/100 mg.

14. The solid dosage form of Claim 1 wherein said water-soluble polymer has a Tg of from about 80 to about 180 °C.

15. The solid dosage form of Claim 1 wherein said water-soluble polymer is a homopolymer or copolymer of N-vinyl pyrrolidone.

16. The solid dosage form of Claim 1 wherein said water-soluble polymer is a copolymer of N-vinyl pyrrolidone and vinyl acetate.

17. The solid dosage form of Claim 1 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

18. The solid dosage form of Claim 1 which contains, upon storage for about 6 weeks at about 40 °C and about 75% humidity, at least about 98 % of the initial content of HIV protease inhibitor.

19. A method of preparing a solid dosage form of claim 1 which comprises:
    i. preparing a homogeneous melt of said HIV protease inhibitor(s), said water-soluble polymer(s) and said surfactant(s), and
    ii. allowing the melt to solidify to obtain a solid dispersion product.

20. The method of claim 19 additionally comprising grinding said solid dispersion product and compressing said solid dispersion product into a tablet.

21. A method of treating an HIV infection comprising administering the solid dosage form of claim 1 to a mammal in need of such treatment.

22. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

a homopolymer of N-vinyl pyrrolidone; and

a sorbitan fatty acid ester.

23. The solid dosage form of Claim 22 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

24. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir);

a copolymer of N-vinyl pyrrolidone; and

a sorbitan fatty acid ester.

25. The solid dosage form of Claim 24 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

26. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir);

a copolymer of N-vinyl pyrrolidone and vinyl acetate; and

a sorbitan fatty acid ester.

27. The solid dosage form of Claim 26 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

28. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) from about 5 % to about 30 % by weight of the dosage form;

a homopolymer of N-vinyl pyrrolidone from about 50 % to about 85 % by weight of the dosage form; and

a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

29. The solid dosage form of Claim 28 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

30. The solid dosage form of claim 29 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight.

31. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir) from about 5 % to about 30 % by weight of the dosage form;

a copolymer of N-vinyl pyrrolidone from about 50 % to about 85 % by weight of the dosage form; and

a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

32. The solid dosage form of Claim 31 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

33. The solid dosage form of claim 32 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight.

34. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(l-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir) present in an amount from about 5 % to about 30 % by weight of the dosage form;

a copolymer of N-vinyl pyrrolidone and vinyl acetate from about 50 % to about 85 % by weight of the dosage form; and

a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

35. The solid dosage form of Claim 34 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

36. The solid dosage form of claim 35 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight of the dosage form.

37. A method of treating an HIV infection comprising administering the solid dosage form of any one of claims 22-36 to a mammal in need of such treatment.

CLAIMS

1. A solid pharmaceutical dosage form comprising:

lopinavir and ritonavir formulated in solid dispersion;

a pharmaceutically acceptable water-soluble polymer having a Tg of at least 50°C, and

a pharmaceutically acceptable surfactant having an HLB value of from 4 to 10.

2. The dosage form of claim 1, wherein said surfactant is selected from polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester or sorbitan fatty acid mono ester.

3. The dosage form of claim 1, wherein said surfactant is selected from polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan mono laurate, sorbitan monooleate, sorbitan monopalnitate or sorbitan stearate.

4. The dosage form of claim 1, wherein said surfactant is a sorbitan fatty acid ester.

5. The dosage form of claim 1, wherein said surfactant is sorbitan monolaurate.

6. The dosage form of claim 1, wherein said water-soluble polymer is selected from homopolymer of N-vinyl lactam, copolymer of N-vinyl lactam, cellulose ester, cellulose ether, polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide or polysaccharide.

7. The dosage form of claim 1, wherein said water-soluble polymer is selected from homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose, hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate, polyethylene oxide, polypropylene oxide, copolymer of ethylene oxide and propylene oxide, methacrylic

acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl acrylate), poly(hydroxyalkyl methacrylate), copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, carrageenan, galactomannan or xanthan gum.

8. The dosage form of claim 1, wherein said water-soluble polymer is a copolymer of N-vinyl pyrrolidone and vinyl acetate.

9. The dosage form of claim 1, wherein said water-soluble polymer is copovidone.

10. The dosage form of claim 1, wherein said water-soluble polymer is selected from the group consisting of homopolymer of N-vinyl lactam, copolymer of N-vinyl lactam, cellulose ester, cellulose ether, polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide and polysaccharide, and wherein said surfactant is selected from the group consisting of polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester and sorbitan fatty acid mono ester.

11. The dosage form of claim 1, wherein said water-soluble polymer is selected from the group consisting of homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose, hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate, polyethylene oxide, polypropylene oxide, copolymer of ethylene oxide and propylene oxide, methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl acrylate), poly(hydroxyalkyl methacrylate), copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, carrageenan, galactomannan and xanthan gum, and wherein said surfactant is selected from the group consisting of polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene

glycol monolaurate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan mono laurate, sorbitan monooleate, sorbitan monopalnitate and sorbitan stearate.

12. The dosage form of claim 1, wherein said water-soluble polymer is a copolymer of N-vinyl pyrrolidone and vinyl acetate, and said surfactant is a sorbitan fatty acid ester.

13. The dosage form of claim 1, wherein said water-soluble polymer is copovidone, and said surfactant is sorbitan monolaurate.

14. The dosage form of claim 1, wherein said ritonavir and lopinavir are formulated in solid or glassy solution.

15. The dosage form of claim 12, wherein said ritonavir and lopinavir are formulated in solid or glassy solution.

16. The dosage form of claim 13, wherein said ritonavir and lopinavir are formulated in solid or glassy solution.

17. The solid dosage form of claim 16 which contains, upon storage for 6 weeks at 40 °C and 75% humidity, at least 98% of the initial content of ritonavir.

18. A solid pharmaceutical dosage form comprising:

lopinavir and ritonavir formulated in solid dispersion;

a pharmaceutically acceptable water-soluble polymer having a Tg of at least 50 °C, and

a combination of surfactants having an HLB value of from 4 to 10.