Claims:

1. A pharmaceutical composition of calanolide, for oral or parenteral administration, comprising:
   a) a calanolide or mixture of calanolides,
   b) one or more solubility enhancers, and
   c) one or more surfactants.

2. The pharmaceutical composition according to claim 1, wherein the said composition has enhanced solubility and bioavailability.

3. The pharmaceutical composition according to claim 2, wherein said composition provides an increase in oral or parenteral bioavailability of calanolide, as measured by $AUC_{(0-24)}$, of at least 20%.

4. The pharmaceutical composition according to claim 2, wherein said composition provides an increase in oral or parenteral bioavailability of calanolide, as measured by C_{max}, of at least 30%

5. The pharmaceutical composition according to claim 2, wherein said composition provides an increase solubility of calanolide of at least 20%.

6. The pharmaceutical composition according to claim 1, wherein said composition is in the form of liquid, semi-solid, or solid.

7. The pharmaceutical composition according to claim 1, wherein:
   a) the calanolide or mixture of calanolides is present in an amount of from about 0.5% to about 80% by weight of the total composition;
   b) the solubility enhancer is present in an amount of from about 0.5% to about 90% by weight of the total composition; and
   c) the surfactant is present in an amount of from about 0.1% to about 80% by weight of the final composition.

8. The pharmaceutical composition according to claim 1, wherein:
   a) the calanolide or mixture of calanolides is present in an amount of from about 5% to about 50% by weight of the total composition;
   b) the solubility enhancer is present in an amount of from about 10% to about 60% by weight of the total composition; and
   c) the surfactant is present in an amount of from about 5% to about 50% by weight of the final composition.

9. The pharmaceutical composition according to claim 1, wherein:
   a) the calanolide or mixture of calanolides is present in an amount of from about 10% to about 35% by weight of the total composition;
   b) the solubility enhancer is present in an amount of from about 25% to about 50% by weight of the total composition; and
   c) the surfactant is present in an amount of from about 20% to about 40% by weight of the final composition.

10. The pharmaceutical composition according to claim 1, wherein the calanolide is selected from the group consisting of calanolides, their derivatives, pharmaceutically acceptable salts, esters, amides, prodrugs, active metabolites, isomers, analogues, and mixtures thereof.

11. The pharmaceutical composition according to claim 1, wherein the calanolide is (+)-calanolide A.

12. The pharmaceutical composition according to claim 1, wherein the calanolide particles present in the composition are in the form of crystalline, semi-crystalline, amorphous, semi-amorphous, liquid, dispersed solid, or combination(s) of form thereof.

13. The pharmaceutical composition according to claim 12, wherein the particle size of the calanolide present in the form of a dispersed solid is selected from the group consisting of particle size of less than 1000 micron or less than 50 micron

or less than 0.1 micron.

14. The pharmaceutical composition according to claim 1, wherein the solubility enhancer is selected from the group consisting of oils, pyrrolidone derivatives, polyglycols, aliphatic amides, polyethers, alcohols, esters of alcohols, dimethyl sulfoxide, cyclodextrins, and combinations thereof.

15. The pharmaceutical composition according to claim 14, wherein the oil is selected from the group consisting of monoglycerides, diglycerides, triglycerides, vegetable oils, animal oils, fatty acids, and combinations thereof.

16. The pharmaceutical composition according to claim 15, wherein the oil is selected from the group consisting of glyceryl monocaprate, glyceryl monocaprylate, glyceryl monostearate, glyceryl monooleate; glyceryl dicaprylate, glyceryl dilaurate, glyceryl tricaprylate, glyceryl tricaprate, glyceryl trimyristate, glyceryl tripalmitate, glyceryl tristearate; almond oil, apricot kernel oil, babassu oil, borage oil, blackcurrant seed oil, canola oil, castor oil, coconut oil, corn oil, cotton seed oil, evening primrose oil, grape seed oil, groundnut oil, mustard seed oil, olive oil, palm oil, palm kernel oil, peanut oil, grape seed oil, rapeseed oil, safflower oil seed, sesame oil, soya bean oil, sunflower seed oil; fish oil, eel oil, fish liver oil, shark oil, mink oil; myristic acid, palmitic acid, eicosapentaenoic acid, docosahexaenoic acid, and mixtures thereof.

17. The pharmaceutical composition according to claim 14, wherein pyrrolidone derivative is selected from the group consisting of 2-pyrrolidone, N-methyl-2-pyrrolidone, N-ethyl-2-pyrrolidone, N-propy-2-pyrrolidone, N-isopropyl-2-pyrrolidone, N-butyl-2-pyrrolidone, polyvinylpyrrolidone K-30, polyvinylpyrrolidone K-90, and mixtures thereof.

18. The pharmaceutical composition according to claim 14, wherein the cyclodextrin is selected from the group consisting of alpha-cyclodextrin, beta-cyclodextrin, gamma-cyclodextrin, hydroxypropyl alpha-cyclodextrin, methylated alpha-

cyclodextrin, methylated beta-cyclodextrin, hydroxyethyl beta-cyclodextrin, hydroxypropyl beta-cyclodextrin, hydroxypropyl gamma-cyclodextrin, and methylated gamma-cyclodextrin, and mixtures thereof.

19. The pharmaceutical composition according to claim 1, wherein the surfactant is selected from the group consisting of nonionic surfactant, anionic surfactant, cationic surfactant, and zwitterionic surfactants, and combinations thereof.

20. The pharmaceutical composition according to claim 19, wherein the nonionic surfactant is selected from the group consisting of polyoxyethylated vegetable oils, polyoxyethylated hydrogenated vegetable oils, polyoxyethylene sorbitan-fatty acid esters, polyoxyethylene fatty acid esters, sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block co-polymers, sucrose fatty acid esters, trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols, and mixtures thereof.

21. The pharmaceutical composition according to claim 20, wherein the nonionic surfactant is selected from the group consisting of PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monooleate, polyoxyethylene 40 stearate, PEG-6 apricot kernel oil, PEG-6 corn oil, sorbitan oleate, sorbitan tristearate, poloxamer 188, sucrose distearate and mixtures thereof.

22. The pharmaceutical composition according to claim 19, wherein the anionic surfactant is selected from the group consisting of sodium oleate, sodium palmitate, sodium lauryl sulfate, sodium dioctyl sulfosuccinate, sodium cholate, and mixtures thereof.

23. The pharmaceutical composition according to claim 19, wherein the cationic surfactant is selected from the group consisting of lauroyl carnitine, cetyl trimethyl ammonium bromide, dodecyl ammonium chloride, betaine, benzalkonium chloride, and mixtures thereof.

24. The pharmaceutical composition according to claim 19, wherein the zwitterionic surfactant is selected from the group consisting of soy lecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, hydrogenated lecithin, and mixtures thereof.

25. The pharmaceutical composition according to claim 1, further comprising at least one pharmaceutically acceptable excipient.

26. The pharmaceutical composition according to claim 1 or 25, wherein said composition is present in a unit dosage form for oral or parenteral administration.

27. The pharmaceutical composition according to claim 26, wherein the unit dosage form for oral administration is selected from the group consisting of soft gelatin capsules, soft carrageenan capsules, soft starch capsules, soft cellulose capsules, hard gelatin capsules, hard carrageenan capsules, hard starch capsules, hard cellulose capsules, tablets, coated tablets, immediate release tablets, sustained release tablets, double-layer tablets with one layer of sustained release and one layer of immediate release, oral liquid preparations, granules, and pellets.

28. The pharmaceutical composition according to claim 26, wherein the unit dosage form for parenteral administration is selected from the group consisting of intramuscular injections, intrathecal injections, intradermal injections, intraperitoneal injections, and subcutaneous injections.

29. The pharmaceutical composition according to claim 1, further comprising at least one additional agent wherein the additional agent is anti-HIV agent, anti-mycobacterial agent, or a combination thereof.

30. The pharmaceutical composition according to claim 29, wherein said at least one additional anti-HIV agent is selected from protease inhibitors, non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, integrase inhibitors, entry and fusion

inhibitors, maturation inhibitors, and combinations thereof.

31. The pharmaceutical composition according to claim 29, wherein the anti-mycobacterial agent is an anti-TB agent.

32. The pharmaceutical composition according to claim 31, wherein the anti-TB agent comprises isoniazid, rifampin, rifabutin, rifapentine, ethambutol, cyclic peptides, ethionamide, fluoroquinolones, pyrazinamide, PAS (*p*-aminosalicylic acid), aminoglycosides, cycloserine, thioamides, linezolid, levofloxacin, ciprofloxacin, moxi-or gatifloxacin, amikacin, kanamycin, streptomycin, capreomycin, viomycin, enviomycin, clarithromycin, thioacetazone, thioridazine, arginine, vitamin D and combinations thereof.

33. A process of preparing the pharmaceutical composition according to claim 1 comprising the steps of:

i) mixing a calanolide or mixture of calanolides with one or more solubility enhancers, at temperature between 20°C to 65°C;

ii) mixing the resulting mixture obtained in step (i) with one or more surfactants to form a homogenous mixture; and

wherein the mixing process in step (i) can further comprise an additional step of grinding the powder mixture in a dispersion mill for 1 to 40 hours.

34. A process of preparing the pharmaceutical composition according to claim 1 comprising the steps of:

i) mixing a calanolide or mixture of calanolides in an amount of from about 0.5% to about 80% by weight of the total composition with one or more solubility enhancers in an amount of from about 0.5% to about 90% by weight of the total composition, at temperature between 20°C to 65°C;

ii) mixing the resulting mixture obtained in step (i) with one or more surfactants in an amount of from about 0.1 % to about 80% to form a homogenous mixture; and

wherein the mixing process in step (i) can further comprise an additional step of

grinding the powder mixture in a dispersion mill for 1 to 40 hours.

35. A process of preparing the pharmaceutical composition according to claim 1 comprising the steps of:

i) mixing a calanolide or mixture of calanolides in an amount of from about 5% to about 50% by weight of the total composition with one or more solubility enhancers in an amount of from about 10% to about 60% by weight of the total composition, at temperature between 20°C to 65°C;

ii) mixing the resulting mixture obtained in step (i) with one or more surfactants in an amount of from about 5 % to about 50% to form a homogenous mixture; and

wherein the mixing process in step (i) can further comprise an additional step of grinding the powder mixture in a dispersion mill for 1 to 40 hours.

36. A process of preparing the pharmaceutical composition according to claim 1 comprising the steps of:

i) mixing a calanolide or mixture of calanolides in an amount of from about 10% to about 35% by weight of the total composition with one or more solubility enhancers in an amount of from about 25% to about 50% by weight of the total composition, at temperature between 20°C to 65°C;

ii) mixing the resulting mixture obtained in step (i) with one or more surfactants in an amount of from about 20 % to about 40% to form a homogenous mixture; and

wherein the mixing process in step (i) can further comprise an additional step of grinding the powder mixture in a dispersion mill for 1 to 40 hours.

37. Use of the pharmaceutical composition according claim 1 in the preparation of a medicament for the treatment and prevention of retroviral diseases especially HIV-1 in mammals.

38. Use of the pharmaceutical composition according to claim 37, wherein the mammal is a human.

39. Use of the pharmaceutical composition according to claim 1 in the preparation of a medicament for the treatment and prevention of mycobacterial diseases especially tuberculosis in mammals.

40. Use of the pharmaceutical composition according to claim 39, wherein the mammal is a human.

41. A pharmaceutical composition according to claim 1 for use in the treatment and prevention of retroviral diseases especially HIV-1 in mammals.

42. A pharmaceutical composition according to claim 41, wherein the mammal is a human.

43. A pharmaceutical composition according to claim 1 for use in the treatment and prevention of mycobacterial diseases especially tuberculosis in mammals.

44. A pharmaceutical composition according to claim 43, wherein the mammal is a human.

Claims:

1. A pharmaceutical composition of calanolide, for oral or parenteral administration, comprising:
   a) a calanolide or mixture of calanolides,
   b) one or more solubility enhancers, and
   c) one or more surfactants.

2. The pharmaceutical composition according to claim 1, wherein the said composition has enhanced solubility and bioavailability when compared to a control composition.

3. The pharmaceutical composition according to claim 2, wherein said composition provides an increase in oral or parenteral bioavailability of calanolide, as measured by $AUC_{(0\text{-}24)}$, of at least 20% when compared to a control composition.

4. The pharmaceutical composition according to claim 2, wherein said composition provides an increase in oral or parenteral bioavailability of calanolide, as measured by C_{max}, of at least 30% when compared to a control composition.

5. The pharmaceutical composition according to claim 2, wherein said composition provides an increase solubility of calanolide of at least 20% when compared to a control composition.

6. The pharmaceutical composition according to claim 1, wherein said composition is in the form of liquid, semi-solid, or solid.

7. The pharmaceutical composition according to claim 1, wherein:
   a) the calanolide or mixture of calanolides is present in an amount of from 0.5% to 80% by weight of the total composition;

b) the solubility enhancer is present in an amount of from 0.5% to 90% by weight of the total composition; and

c) the surfactant is present in an amount of from 0.1% to 80% by weight of the final composition.

8. The pharmaceutical composition according to claim 1, wherein:

a) the calanolide or mixture of calanolides is present in an amount of from 5% to 50% by weight of the total composition;

b) the solubility enhancer is present in an amount of from 10% to 60% by weight of the total composition; and

c) the surfactant is present in an amount of from 5% to 50% by weight of the final composition.

9. The pharmaceutical composition according to claim 1, wherein:

a) the calanolide or mixture of calanolides is present in an amount of from 10% to 35% by weight of the total composition;

b) the solubility enhancer is present in an amount of from 25% to 50% by weight of the total composition; and

c) the surfactant is present in an amount of from 20% to 40% by weight of the final composition.

10. The pharmaceutical composition according to claim 1, wherein the calanolide is selected from the group consisting of calanolides, their derivatives, pharmaceutically acceptable salts, esters, amides, prodrugs, active metabolites, isomers, analogues, and mixtures thereof.

11. The pharmaceutical composition according to claim 1, wherein the calanolide is (+)-calanolide A.

12. The pharmaceutical composition according to claim 1, wherein the calanolide particles present in the composition are in the form of crystalline, semi-

crystalline, amorphous, semi-amorphous, liquid, dispersed solid, or combination(s) of form thereof.

13. The pharmaceutical composition according to claim 12, wherein the particle size of the calanolide present in the form of a dispersed solid is selected from the group consisting of particle size of less than 1000 micron or less than 50 micron or less than 0.1 micron.

14. The pharmaceutical composition according to claim 1, wherein the solubility enhancer is selected from the group consisting of oils, pyrrolidone derivatives, polyglycols, aliphatic amides, polyethers, alcohols, esters of alcohols, dimethyl sulfoxide, cyclodextrins, and combinations thereof.

15. The pharmaceutical composition according to claim 14, wherein the oil is selected from the group consisting of monoglycerides, diglycerides, triglycerides, vegetable oils, animal oils, fatty acids, and combinations thereof.

16. The pharmaceutical composition according to claim 15, wherein the oil is selected from the group consisting of glyceryl monocaprate, glyceryl monocaprylate, glyceryl monostearate, glyceryl monooleate; glyceryl dicaprylate, glyceryl dilaurate; glyceryl tricaprylate, glyceryl tricaprate, glyceryl trimyristate, glyceryl tripalmitate, glyceryl tristearate; almond oil, apricot kernel oil, babassu oil, borage oil, blackcurrant seed oil, canola oil, castor oil, coconut oil, corn oil, cotton seed oil, evening primrose oil, grape seed oil, groundnut oil, mustard seed oil, olive oil, palm oil, palm kernel oil, peanut oil, grape seed oil, rapeseed oil, safflower oil seed, sesame oil, soya bean oil, sunflower seed oil; fish oil, eel oil, fish liver oil, shark oil, mink oil; myristic acid, palmitic acid, eicosapentaenoic acid, docosahexaenoic acid, and mixtures thereof.

17. The pharmaceutical composition according to claim 14, wherein pyrrolidone derivative is selected from the group consisting of 2-pyrrolidone, N-methyl-2-

pyrrolidone, N-ethyl-2-pyrrolidone, N-propyl-2-pyrrolidone, N-isopropyl-2-pyrrolidone, N-butyl-2-pyrrolidone, polyvinylpyrrolidone K-30, polyvinylpyrrolidone K-90, and mixtures thereof.

18. The pharmaceutical composition according to claim 14, wherein the cyclodextrin is selected from the group consisting of alpha-cyclodextrin, beta-cyclodextrin, gamma-cyclodextrin, hydroxypropyl alpha-cyclodextrin, methylated alpha-cyclodextrin, methylated beta-cyclodextrin, hydroxyethyl beta-cyclodextrin, hydroxypropyl beta-cyclodextrin, hydroxypropyl gamma-cyclodextrin, and methylated gamma-cyclodextrin, and mixtures thereof.

19. The pharmaceutical composition according to claim 1, wherein the surfactant is selected from the group consisting of nonionic surfactants, anionic surfactants, cationic surfactants, and zwitterionic surfactants, and combinations thereof.

20. The pharmaceutical composition according to claim 19, wherein the nonionic surfactant is selected from the group consisting of polyoxyethylated vegetable oils, polyoxyethylated hydrogenated vegetable oils, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block co-polymers, sucrose fatty acid esters, trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols, and mixtures thereof.

21. The pharmaceutical composition according to claim 20, wherein the nonionic surfactant is selected from the group consisting of PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monooleate, polyoxyethylene 40 stearate, PEG-6 apricot kernel oil, PEG-6 corn oil, sorbitan oleate, sorbitan tristearate, poloxamer 188, sucrose distearate and mixtures thereof.

22. The pharmaceutical composition according to claim 19, wherein the anionic surfactant is selected from the group consisting of sodium oleate, sodium palmitate, sodium lauryl sulfate, sodium dioctyl sulfosuccinate, sodium cholate, and mixtures thereof.

23. The pharmaceutical composition according to claim 19, wherein the cationic surfactant is selected from the group consisting of lauroyl carnitine, cetyl trimethyl ammonium bromide, dodecyl ammonium chloride, betaine, benzalkonium chloride, and mixtures thereof.

24. The pharmaceutical composition according to claim 19, wherein the zwitterionic surfactant is selected from the group consisting of soy lecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, hydrogenated lecithin, and mixtures thereof.

25. The pharmaceutical composition according to claim 1, further comprising at least one pharmaceutically acceptable excipient.

26. The pharmaceutical composition according to claim 1 or 25, wherein said composition is present in a unit dosage form for oral or parenteral administration.

27. The pharmaceutical composition according to claim 26, wherein the unit dosage form for oral administration is selected from the group consisting of soft gelatin capsules, soft carrageenan capsules, soft starch capsules, soft cellulose capsules, hard gelatin capsules, hard carrageenan capsules, hard starch capsules, hard cellulose capsules, tablets, coated tablets, immediate release tablets, sustained release tablets, double-layer tablets with one layer of sustained release and one layer of immediate release, oral liquid preparations, granules, and pellets.

28. The pharmaceutical composition according to claim 26, wherein the unit dosage form for parenteral administration is selected from the group consisting of

intramuscular injections, intrathecal injections, intradermal injections, intraperitoneal injections, and subcutaneous injections.

29. The pharmaceutical composition according to claim 1, further comprising at least one additional agent wherein the additional agent is anti-HTV agent, anti-mycobacterial agent, or a combination thereof.

30. The pharmaceutical composition according to claim 29, wherein the said at least one additional anti-HIV agent is selected from protease inhibitors, non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, integrase inhibitors, entry and fusion inhibitors, maturation inhibitors, and combinations thereof.

31. The pharmaceutical composition according to claim 29, wherein the anti-mycobacterial agent is an anti-TB agent.

32. The pharmaceutical composition according to claim 31, wherein the anti-TB agent comprises isoniazid, rifampin, rifabutin, rifapentine, ethambutol, cyclic peptides, ethionamide, fluoroquinolones, pyrazinamide, PAS (*p*-aminosalicylic acid), aminoglycosides, cycloserine, thioamides, linezolid, levofloxacin, ciprofloxacin, moxi-or gatifloxacin, amikacin, kanamycin, streptomycin, capreomycin, viomycin, enviomycin, clarithromycin, thioacetazone, thioridazine, arginine, vitamin D and combinations thereof.

33. A process of preparing the pharmaceutical composition according to claim 1, comprising the steps of:

i) mixing a calanolide or mixture of calanolides with one or more solubility enhancers, at temperature between 20°C to 65°C to form a powder mixture;

ii) mixing the resulting mixture obtained in step (i) with one or more surfactants to form a homogenous mixture; and

wherein the mixing process in step (i) can further comprise an additional step of grinding the powder mixture in a dispersion mill for 1 to 40 hours.

34. A process of preparing the pharmaceutical composition according to claim 1, comprising the steps of:

i) mixing a calanolide or mixture of calanolides in an amount of from 0.5% to 80% by weight of the total composition with one or more solubility enhancers in an amount of from 0.5% to 90% by weight of the total composition, at temperature between 20°C to 65°C to form a powder mixture;

ii) mixing the resulting mixture obtained in step (i) with one or more surfactants in an amount of from 0.1 % to 80% to form a homogenous mixture; and

wherein the mixing process in step (i) can further comprise an additional step of grinding the powder mixture in a dispersion mill for 1 to 40 hours.

35. A process of preparing the pharmaceutical composition according to claim 1, comprising the steps of:

i) mixing a calanolide or mixture of calanolides in an amount of from 5% to 50% by weight of the total composition with one or more solubility enhancers in an amount of from 10% to 60% by weight of the total composition, at temperature between 20°C to 65 °C to form a powder mixture;

ii) mixing the resulting mixture obtained in step (i) with one or more surfactants in an amount of from 5 % to 50% to form a homogenous mixture; and

wherein the mixing process in step (i) can further comprise an additional step of grinding the powder mixture in a dispersion mill for 1 to 40 hours.

36. A process of preparing the pharmaceutical composition according to claim 1 comprising the steps of:

i) mixing a calanolide or mixture of calanolides in an amount of from 10% to 35% by weight of the total composition with one or more solubility enhancers in an amount of from 25% to 50% by weight of the total composition, at temperature between 20°C to 65°C to form a powder mixture;

ii) mixing the resulting mixture obtained in step (i) with one or more surfactants in an amount of from 20 % to 40% to form a homogenous mixture; and

wherein the mixing process in step (i) can further comprise an additional step of grinding the powder mixture in a dispersion mill for 1 to 40 hours.

37. Use of the pharmaceutical composition according to claim 1 in the preparation of a medicament for the treatment and prevention of retroviral diseases especially HIV-1 in mammals.

38. Use of the pharmaceutical composition according to claim 37, wherein the mammal is a human.

39. Use of the pharmaceutical composition according to claim 1 in the preparation of a medicament for the treatment and prevention of mycobacterial diseases especially tuberculosis in mammals.

40. Use of the pharmaceutical composition according to claim 39, wherein the mammal is a human.

41. A pharmaceutical composition according to claim 1 for use in the treatment and prevention of retroviral diseases especially HIV-1 in mammals.

42. A pharmaceutical composition according to claim 41, wherein the mammal is a human.

43. A pharmaceutical composition according to claim 1 for use in the treatment and prevention of mycobacterial diseases especially tuberculosis in mammals.

44. A pharmaceutical composition according to claim 43, wherein the mammal is a human.