cyclosporin in solution which have a higher emulsion stability. For example, there is a need for emulsions where the length of time for crystal formation or precipitation to occur is longer.

[0010] Formulating an active ingredient into a bead by passing a composition comprising a water-soluble polymer matrix in which are dispersed droplets of oil through a single orifice nozzle is disclosed in WO2010/133609. Solid cyclosporin formation in an emulsion is particularly undesirable whilst forming beads from an emulsion comprising solid cyclosporin. This is because solid cyclosporin is less active at an intended therapeutic site, for example the gastrointestinal tract, than solubilised cyclosporin. The problem of cyclosporin crystallising or precipitating is particularly relevant in scale up production of beads from the emulsion. Scaling up production of beads results in batches of the emulsion being kept for longer periods and the propensity for crystallisation or precipitation to happen increasing. Therefore, there is a need for an emulsion with a high stability to reduce the amount of solid in the emulsion whilst being processed into beads and consequently to reduce the amount of solid in the bead.

[0011] Similarly there is a need for a component of the emulsion to inhibit crystallisation or precipitation.

SUMMARY

[0011a] In one aspect, the present disclosure refers to a solid colloidal oral composition comprising a continuous phase which comprises a hydrogel-forming polymer matrix and a disperse phase which comprises cyclosporin and an oil phase, wherein the composition further comprises a surfactant comprising a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise a polyethylene glycol ether or ester; wherein the hydrogel-forming polymer matrix is in an amount of at least 25% by weight based upon the dry weight of the composition; and wherein the hydrogel forming polymer matrix comprises one or more of gelatin, agar, starch, casein, chitosan, soya bean protein, safflower protein, alginates, gellan gum, carrageenan, xanthan gum, phthalated gelatin, succinated gelatin, cellulosephthalate-acetate, oleoresin, polyvinylacetate, polymerisates of acrylic or methacrylic esters, polyvinylacetate-phthalate.

[0011b] In another aspect, the present disclosure refers to a multiple mini bead formulation, comprising a unit dosage form comprising a multiplicity of mini beads disclosed herein.

[0011c] In yet another aspect, the present disclosure refers to a colloidal composition comprising

a continuous phase comprising:
a hydrogel forming polymer matrix comprising gelatin in an amount of 300 to 700 mg/g;
a disperse phase comprising:
cyclosporin in an amount of up to 200 mg/g; and
a medium chain tri-glyceride in an amount of 20 to 200 mg/g;
and the composition further comprising:
solvent in an amount of 100 to 250 mg/g;
surfactant having an HLB of up to 8 in an amount of 80 to 200 mg/g, wherein the surfactant comprises a medium or long chain fatty acid mono- or di-glyceride or a combination thereof which

does not comprise a polyethylene glycol ether or ester, for example glyceryl caprylate, glyceryl caprate, glyceryl monooleate, glyceryl dioleate, glycerol monolinoleate or a combination thereof; and anionic surfactant in an amount of up to 50 mg/g.

[0011d] In yet another aspect, the present disclosure refers to a composition comprising cyclosporin A and a surfactant, wherein the surfactant comprises a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise a polyethylene glycol ether or ester and after oral administration of the composition to a human the mean concentration of cyclosporin A: the concentration of cyclosporin A metabolites in a faecal sample from the human is greater than 12:1.

[0011e] In yet another aspect, the present disclosure refers to a process for making a composition, the process comprising mixing an oil phase with an aqueous phase, wherein the aqueous phase comprises a hydrogel forming polymer present in an amount of at least 25% by weight of the composition based upon the dry weight of the composition, wherein the hydrogel forming polymer matrix comprises one or more of gelatin, agar, starch, casein, chitosan, soya bean protein, safflower protein, alginates, gellan gum, carrageenan, xanthan gum, phthalated gelatin, succinated gelatin, cellulosephthalate-acetate, oleoresin, polyvinylacetate, polymerisates of acrylic or methacrylic esters, polyvinylacetate-phthalate, wherein the oil phase has cyclosporin in solution and comprises a surfactant comprising a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and not comprising a polyethylene glycol ether or ester.

[0011f] In yet another aspect, the present disclosure refers to the use of a composition disclosed herein in the manufacture of a medicament for treating a condition, wherein the condition is a condition of the gastrointestinal tract; optionally wherein the condition is selected from inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, ulcerative colitis, celiac disease, graft vs host disease, gastrointestinal graft-versus-host disease, gastroenteritis, duodenitis, jejunitis, ileitis, peptic ulcer, pouchitis, Curling's ulcer, appendicitis, colitis, pseudomembraneous colitis, diverticulosis, diverticulitis, microscopic colitis, collagenous colitis, lymphocytic colitis, colorectal carcinoma, adenocarcinoma, myasthenia gravis, stomach ulcers, proctitis, mucositis, chemotherapy-associated enteritis, radiation-associated enteritis, short bowel disease, or chronic diarrhea, endometriosis, inflammatory disorders such as diversion colitis, ischemic colitis, infectious colitis, chemical colitis, fulminant colitis, autistic enterocolitis, interdeminate colitis, jejunoiletis, atypical colitis, fulminant colitis, autistic enterocolitis, interdeminate colitis, jejunoiletis, ileocolitis or granulomatous colitis, the prevention of rejection following bone marrow transplantation, psoriasis, atopic dermatitis, rheumatoid arthritis, nephrotic syndrome primary sclerosing cholangitis, familial adenomatous polyposis, or perianal Crohn's, including perianal fistulae.

[0012] It has surprisingly been found that a surfactant has a stabilising effect on an emulsion comprising cyclosporin in solution. The surfactant may comprise or may be a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof, optionally wherein the surfactant does not comprise or is not a polyethyleneglycol ether or ester. The surfactant may have an HLB of up to 10, preferably of up to 7 or up to 5. Specifically, it has been found that a medium chain or long chain fatty acid mono-or di-glyceride or a combination thereof, optionally not comprising or being a polyethyleneglycol ether or ester, has a stabilising effect on an emulsion comprising cyclosporin in solution. The emulsion may be an oil-in-water emulsion.

[0013] A medium chain or long chain fatty acid mono- or di-glyceride is an ester of such a fatty acid and glycerol, wherein there may be one (mono-) or two (di-) fatty acids esterified to glycerol. The glycerol may consist of one glycerol for example mono glycerol (a mono-glycerol ester is also be referred to as a glyceride).

[0014] It has been found that the use of certain surfactants during the manufacture of the compositions are particularly effective in stabilising the colloid (for example emulsion), resulting from the mixing of an aqueous solution comprising a hydrogel forming polymer and an oil phase comprising cyclosporin A. When the colloid comprises an oil-in-water emulsion, it has been found that the presence of a surfactant having an HLB of up to 8 (particularly up to 6 or from 2 to 6) in the oil phase is particularly effective in stabilising the emulsion in particular during the preparation of the composition. The presence of such surfactants has been found to inhibit the formation of cyclosporin A crystals after the formation of the colloid (oil-in-water emulsion). The presence of a surfactant with an HLB of up to 10 maintains the cyclosporin A in solution in the oil phase during manufacture and may also provide favourable release of the cyclosporin A in a solubilised form from the composition

CLAIMS

1. A solid colloidal oral composition comprising a continuous phase which comprises a hydrogel-forming polymer matrix and a disperse phase which comprises cyclosporin and an oil phase , wherein the composition further comprises a surfactant comprising a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise a polyethylene glycol ether or ester; wherein the hydrogel-forming polymer matrix is in an amount of at least 25% by weight based upon the dry weight of the composition; and wherein the hydrogel forming polymer matrix comprises one or more of gelatin, agar, starch, casein, chitosan, soya bean protein, safflower protein, alginates, gellan gum, carrageenan, xanthan gum, phthalated gelatin, succinated gelatin, cellulosephthalate-acetate, oleoresin, polyvinylacetate, polymerisates of acrylic or methacrylic esters, polyvinylacetate-phthalate.

2. The composition of claim 1 wherein the oil phase comprises a solution of the cyclosporin.

3. The composition of claim 1 or claim 2, wherein the surfactant is present in an amount of more than 6 wt% of the dry weight of the composition.

4. The composition of any of claims 1 to 3, wherein the surfactant is non-ionic; and/or the surfactant comprises a long chain fatty acid mono- or di-glyceride or a combination thereof.

5. The composition of any of claims 1 to 3, wherein the surfactant comprises a surfactant selected from:

   glyceryl monocaprate, glyceryl dicaprate, glyceryl monocaprylate, glyceryl dicaprylate, glyceryl caprate, glyceryl monocaprylate/caprate, glyceryl caprylate/caprate, glyceryl dicaprylate/caprate, glyceryl monooleate/dioleate, glyceryl monooleate, glyceryl dioleate, glyceryl monostearate, glyceryl distearate, glyceryl monopalmitostearate, glyceryl dipalmitostearate, glyceryl monobehenate, glyceryl dibehenate, glyceryl monolinoleate, glycerol monolinoleate, glyceryl dilinoleate, polyglyceryl dioleate, propylene glycol monoheptanoate, polyglycerol dioleate, and a combination thereof; optionally

   wherein the surfactant is selected from: glyceryl monocaprylate/caprate, glyceryl dicaprylate/caprate, glyceryl monooleate, glycerol monolinoleate, glyceryl dioleate, glyceryl monostearate, glyceryl distearate, glyceryl monopalmitostearate, glyceryl dipalmitostearate, glyceryl monobehenate, glyceryl dibehenate, glyceryl monolinoleate, glyceryl dilinoleate, polyglyceryl dioleate and a combination thereof.

6. The composition of any of claims 1 to 3, wherein the surfactant comprises a surfactant selected from: glyceryl caprylate/caprate, glyceryl monooleate/dioleate, glycerol monolinoleate and a combination thereof.

7. The composition of any preceding claim, wherein the oil phase comprises a liquid lipid and optionally wherein the liquid lipid comprises a glyceride composition,
   further optionally wherein the liquid lipid comprises a medium chain fatty acid triglyceride or a combination thereof, or the liquid lipid comprises a caprylic/capric triglyceride composition.

8. The composition of any preceding claim, wherein the composition further comprises a solvent, wherein the solvent is miscible with the oil phase and water, optionally wherein the solvent is selected from 2-(2-ethoxyethoxy)ethanol and a poly(ethylene glycol), particularly wherein the solvent is 2-(2-ethoxyethoxy)ethanol.

9. The composition of any preceding claim wherein the hydrogel forming polymer matrix comprises a hydrocolloid selected from carrageenan, gelatin, agar and pectin, or a combination thereof; optionally selected from gelatin and agar or a combination thereof, more optionally the polymer of the hydrogel forming polymer matrix comprises gelatin.

10. The composition of any preceding claim, wherein the hydrogel forming polymer matrix further comprise a plasticiser, optionally a plasticiser selected from glycerin, a polyol for example sorbitol, polyethylene glycol and triethyl citrate or a mixture thereof, particularly sorbitol.

11. The composition of any preceding claim, wherein the composition has the characteristics of a composition formed by mixing an aqueous phase premix with an oil phase premix to form a mixture, the aqueous phase premix comprising the hydrogel forming polymer matrix and the oil phase premix comprising the oil phase in which the cyclosporin is dissolved and the surfactant, wherein the mixture is in the form of an emulsion, and allowing the mixture to solidify, wherein the mixture is passed through a single orifice nozzle before being allowed to solidify.

12. The composition of any preceding claim, wherein the composition is a solid composition and further comprises at least one coating, optionally wherein the at least one coating is an outer coating (a second coating).

13. The solid composition of claim 12 wherein the at least one coating is adapted to release the cyclosporin in at least the colon; and/or the at least one coating comprises a pH-independent coating e.g. ethylcellulose.

14. The solid composition of any of claims 12 to 13, wherein the composition comprises two coatings, a first coating and a second coating; optionally wherein the composition comprises a first coating which comprises a water-soluble cellulose ether, for example hydroxypropylmethyl cellulose, and a second coating as specified in any of claims 11 to 12.

15. The composition of any of claims 1 to 14, wherein the composition is a solid composition that is in the form of a minibead optionally having a size of from 0.5mm to 5mm.

16. A multiple mini bead formulation, comprising a unit dosage form comprising a multiplicity of mini beads of claim 15.

17. A colloidal composition comprising
    a continuous phase comprising:
    a hydrogel forming polymer matrix comprising gelatin in an amount of 300 to 700 mg/g;
    a disperse phase comprising:
    cyclosporin in an amount of up to 200 mg/g; and
    a medium chain tri-glyceride in an amount of 20 to 200 mg/g;

and the composition further comprising:

solvent in an amount of 100 to 250 mg/g;

surfactant having an HLB of up to 8 in an amount of 80 to 200 mg/g, wherein the surfactant comprises a medium or long chain fatty acid mono- or di-glyceride or a combination thereof which does not comprise a polyethylene glycol ether or ester, for example glyceryl caprylate, glyceryl caprate, glyceryl monooleate, glyceryl dioleate, glycerol monolinoleate or a combination thereof; and

anionic surfactant in an amount of up to 50 mg/g.

18. A composition comprising cyclosporin A and a surfactant, wherein the surfactant comprises a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise a polyethylene glycol ether or ester and after oral administration of the composition to a human the mean concentration of cyclosporin A: the concentration of cyclosporin A metabolites in a faecal sample from the human is greater than 12:1.

19. The composition of claim 18, wherein the composition comprises a composition according to any of claims 1 to 17.

20. The composition of claim 13, wherein the composition releases less than 15% (for example 0 to 10%) of the cyclosporin A after 2 hours; releases 10% to 40% (for example 10% to 35%, or suitably 15% to 35%) of the cyclosporin A at 4 hours; and releases from about 30% to 70% (for example 40% to 70%) of the cyclosporin A between 4 hours and 12 hours, when measured in a two stage dissolution test using a USP Apparatus II with a paddle speed of 75 rpm and a dissolution medium temperature of 37^{o}C; wherein for the first 2 hours of the dissolution test the dissolution medium is 750 ml of 0.1 N HCl, and at 2 hours 250 ml of 0.2M tribasic sodium phosphate containing 2% SDS is added to the dissolution medium and the pH is adjusted to pH 6.8.

21. The composition of any preceding claim, further comprising a P450 inhibitor or a PgP inhibitor, or a combination thereof.

22. A process for making a composition, the process comprising mixing an oil phase with an aqueous phase, wherein the aqueous phase comprises a hydrogel forming polymer present in an amount of at least 25% by weight of the composition based upon the dry weight of the composition, wherein the hydrogel forming polymer matrix comprises one or more of gelatin, agar, starch, casein, chitosan, soya bean protein, safflower protein, alginates, gellan gum, carrageenan, xanthan gum, phthalated gelatin, succinated gelatin, cellulosephthalate-acetate, oleoresin, polyvinylacetate, polymerisates of acrylic or methacrylic esters, polyvinylacetate-phthalate, wherein the oil phase has cyclosporin in solution and comprises a surfactant comprising a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and not comprising a polyethylene glycol ether or ester.

23. The process of claim 22, wherein the oil phase and the aqueous phase are mixed in a oil phase to aqueous phase ratio of from 1:2 to 1:12; and/or mixing the oil phase with the aqueous phase forms an emulsion; and/or the process further comprises causing the emulsion to solidify.

24. Use of a composition of any of claims 1 to 19 in the manufacture of a medicament for treating a condition, wherein the condition is a condition of the gastrointestinal tract; optionally wherein the condition is selected from inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, ulcerative colitis, celiac disease, graft vs host disease, gastrointestinal graft-versus-host disease, gastroenteritis, duodenitis, jejunitis, ileitis, peptic ulcer, pouchitis, Curling's ulcer, appendicitis, colitis, pseudomembraneous colitis, diverticulosis, diverticulitis, microscopic colitis, collagenous colitis, lymphocytic colitis, colorectal carcinoma, adenocarcinoma, myasthenia gravis, stomach ulcers, proctitis, mucositis, chemotherapy-associated enteritis, radiation-associated enteritis, short bowel disease, or chronic diarrhea, endometriosis, inflammatory disorders such as diversion colitis, ischemic colitis, infectious colitis, chemical colitis, fulminant colitis, autistic enterocolitis, interdeminate colitis, jejunoiletis, atypical colitis, fulminant colitis, autistic enterocolitis, interdeminate colitis, jejunoiletis, ileocolitis or granulomatous colitis, the prevention of rejection following bone marrow transplantation, psoriasis, atopic dermatitis, rheumatoid arthritis, nephrotic syndrome primary sclerosing cholangitis, familial adenomatous polyposis, or perianal Crohn's, including perianal fistulae.