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.

BRIEF SUMMARY OF THE DISCLOSURE

[0011a] In one aspect, the present invention provides a solid oral composition comprising cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix, wherein the surfactant comprises or is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not 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 invention provides 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 invention provides 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 or is 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 invention provides a composition comprising cyclosporin A and a surfactant, wherein the surfactant comprises or is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not 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 invention provides 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 or being a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and not comprising or not being a polyethylene glycol ether or ester.

[0011f] In yet another aspect, the present invention provides 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.

[0011g] In yet another aspect, the present invention provides a liquid composition comprising an aqueous phase, a surfactant and an oil phase in which cyclosporin is dissolved, wherein the oil phase comprises a liquid lipid and the surfactant comprises or is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethylene glycol ether or ester, the aqueous phase comprises a hydrogel-forming polymer and the oil phase is

dispersed in the aqueous phase; wherein the hydrogel-forming polymer is in an amount of at least 25% by weight based upon the dry weight of the composition.

[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

following oral administration of the composition to a subject. Compositions comprising a surfactant of the disclosure with an HLB of up to 8 in at least the oil phase may exhibit high rates of release and/or extent of release of cyclosporin A from the composition compared to the use of surfactants with a higher HLB value in the oil phase. The presence of a surfactant with an HLB of up to 8 in at least the oil phase in the composition may inhibit the precipitation of cyclosporin A after release of the cyclosporin from the composition thereby retaining higher levels of cyclosporin in a solubilised form within the GI tract, for example in the colon. The compositions described herein wherein the composition comprises an oil phase and a surfactant having an HLB of up to 10 form a further independent example of the disclosure.

[0015] Accordingly, there is provided a use of a surfactant for stabilising an emulsion. Preferably, the emulsion is an oil in water emulsion. The surfactant preferably is or comprises 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.

[0016] By the phrase "the surfactant stabilises the emulsion", it is meant that the surfactant increases the length of time for solid particles (for example precipitation or crystallisation) to occur in an emulsion comprising cyclosporin in solution.

[0017] It has also been found that a surfactant inhibits crystallisation of cyclosporin from a cyclosporin solution in an oil phase in an oil-in-water emulsion. The surfactant is or comprises 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. Accordingly, the use of the surfactant provides an emulsion that is free of crystals or precipite for a longer period than prior art emulsions. An emulsion that takes longer for crystallisation or precipitation to occur is beneficial for large-scale bead production. Consequently, the disclosure contemplates a process utilising an emulsion comprising the surfactant to produce beads, particularly in scale up of the bead production process.

[0018] Ordinarily surfactants with a low HLB value, for example up to 8, are used as water-in-oil emulsifiers. As part of the disclosure it has been found that a surfactant is an emulsifier for oil-in-water emulsions comprising dissolved cyclosporin, wherein the surfactant has a HLB value of up to 8 and is or comprises 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.

[0019] Also disclosed is a liquid composition comprising an aqueous phase, a surfactant and an oil phase in which cyclosporin is dissolved. The surfactant may comprise or be a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethyleneglycol ether or ester. The aqueous phase may comprise a hydrogel forming polymer. The oil phase may be dispersed in the aqueous phase. The oil phase may be dispersed in the aqueous phase in the form of a colloid, for example a liquid-liquid colloid. The oil phase may be dispersed in the aqueous phase in the form of an emulsion. Accordingly, the liquid composition may be a liquid emulsion composition.

[0020] The liquid composition may be converted into a solid form by allowing the hydrogel forming polymer to form a hydrogel matrix. There is also provided a process for converting the liquid composition into a bead, wherein the liquid composition is ejected through a single orifice nozzle.

[0021] Also disclosed is provided a composition comprising cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix. The surfactant may be or may comprise a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and may not comprise or may not be a polyethyleneglycol ether or ester. The composition may be a solid composition. The composition may be in the form of a dried bead. The composition may be in the form of a dried colloid.

[0022] Advantageously an enhanced release profile is provided by the presence of the surfactant being or comprising a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof that does not comprise or is not a polyethyleneglycol ether or ester in compositions of the disclosure compared to compositions with a different surfactant. A solid composition of the disclosure exhibits a release profile with higher release of cyclosporin and maintenance of high cyclosporin levels in solution when compared to compositions with a different surfactant (Kolliphor EL, a polyethoxylated castor oil). The dissolution may be measured in deionised water.

[0023] Optionally, the cyclosporin, the hydrogel forming polymer matrix, the surfactant and the oil phase are comprised within a core. Thus, the composition may comprise a core. Accordingly, the composition may comprise a core, wherein the core comprises cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix, wherein the surfactant may be or comprise a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethyleneglycol ether or ester.

[0024] The liquid composition may be a colloid, i.e. it may be a colloidal liquid composition. The composition may be a solid colloid or the composition may be in the form of a solid colloid, i.e. it may be a solid colloidal composition. The colloidal liquid composition of the disclosure may comprise a continuous phase which is or comprises a hydrogel-forming polymer and a disperse phase which is or comprises cyclosporin A and an oil phase, wherein the colloidal liquid composition or the solid colloidal composition further comprise a surfactant (also referred to as a first surfactant) comprising or being a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and not comprising or not being a polyethyleneglycol ether or ester.

[0025] The solid colloidal composition of the disclosure may comprise a continuous phase which is or comprises a hydrogel-forming polymer matrix and a disperse phase which is or comprises cyclosporin A and an oil phase, wherein the colloidal liquid composition or the solid colloidal composition further comprise a surfactant (also referred to as a first surfactant) comprising or being a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and not comprising or not being a polyethyleneglycol ether or ester.

[0026] Throughout the specification both the liquid composition and the composition are referred to by "composition". Furthermore, where an example or aspect is referred to as a "composition" this

may optionally be referring to a liquid composition (for example a colloidal liquid composition) and/or to a solid composition (for example a solid colloidal composition).

[0027] In an example the oil phase comprises a solution of the cyclosporin. As such, the cyclosporin may be dissolved in the oil phase, for example completely dissolved, substantially completely dissolved, or partially dissolved. Thus, the oil phase may comprise a solution of cyclosporin and some undissolved cyclosporin.

[0028] Throughout this specification the term cyclosporin may be referring to the class of compounds or to cyclosporin A. Preferably, the use of cyclosporin is in reference to cyclosporin A.

[0029] The cyclosporin is suitably present in the composition in an amount of from about 5% to about 20%, from about 8% to about 15%, or from about 9% to about 14% by weight based upon the dry weight of the core or of the composition.

[0030] The cyclosporin is suitably present in the liquid composition in an amount of up to 10%, optionally from about 1% to about 10%, from about 2% to about 8%, from about 3% to about 6%, from about 3% to about 5% by weight of the liquid composition. Optionally the cyclosporin may be present in the liquid composition in about 4% by weight of the liquid composition.

[0031] A medium chain fatty acid mono-ester or di-ester comprises a fatty acid having 8 to 12 in chain carbon atoms. A long chain fatty acid mono-ester or di-ester comprises a fatty acid having at least 13 in chain carbon atoms, preferably 13 to 26 in chain carbon atoms. The long chain fatty acid may optionally have from 14 to 22 in chain carbon atoms or 16 to 20 in chain carbon atoms.

[0032] Preferably, the surfactant is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof that does not comprise or is not a polyethyleneglycol ether or ester. Where the surfactant comprises a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof that does not comprise or is not a polyethyleneglycol ether or ester, the medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof is substantially all of the surfactant. For example, the surfactant may comprise medium chain or long chain fatty acid mono -or di-glyceride or a combination thereof that does not comprise or is not a polyethyleneglycol ether or ester in an amount of greater than 80% of the surfactant, optionally greater than 85%, 90%, 95%, 97%, 98% or 99%. Suitably, the surfactant is substantially free of a triglyceride. For example, the surfactant may comprise less than 10%, 8%, 5%, 3%, 2% or 1% of a triglyceride.

[0033] The presence of the surfactant may enhance the rate and or extent of release of cyclosporin from the composition following oral administration. The presence of the surfactant may act to maintain a high proportion of the cyclosporin in a solubilised form after it has been released from the composition into an aqueous medium such as that found in the lower GI tract, particularly the colon.

[0034] The surfactant may have an HLB value of up to 8, up to 6, or up to 5. Alternatively the surfactant may have an HLB value selected from: up to 7, 1-8, 1-7, 2-6, 1-5, 2-5, 1-4, 1-3, 1-2, 2-4, 3-4, 3-6, 5-8, 6-8 and 6-7. Preferably, the surfactant has an HLB value of up to 6, 2-6 or 3-6.

polyethyleneglycol ether or ester, wheren the fatty acid has a chain length of 13 to 22 carbon atoms, optionally 16 to 20 carbon atoms. In particular the fatty acid may have a chain length of 18 carbon atoms.

[0042] In an example the surfactant is 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, glycerol monolinoleate, glyceryl dilinoleate, polyglyceryl dioleate, propylene glycol monoheptanoate, and a combination thereof.

[0043] A preferred surfactant may be or comprise a surfactant 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.

[0044] Accordingly, there is provided a composition comprising cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix, wherein the surfactant may be or may comprise a surfactant 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.

[0045] The surfactant may comprise or be a surfactant selected from: glyceryl caprylate, glyceryl caprate, glyceryl monooleate, glyceryl dioleate, glycerol monolinoleate or a combination thereof.

[0046] A particularly preferred surfactant may be or comprise a surfactant selected from: glyceryl caprylate/caprate (Capmul MCM), glyceryl monooleate/dioleate (Capmul GMO-50) and glycerol monolinoleate (Maisine 35-1).

[0047] Optionally, the surfactant is not a mixture of glyceryl monostearate EP/NF and PEG-75 palmitostearate (for example Gelto™ 64). Suitably, the surfactant may not be or comprise a mixture of glyceryl monostearate.

[0048] In an example the oil phase comprises an oil or liquid lipid and the surfactant is present in an amount greater than the oil or liquid lipid. Optionally, the surfactant may be present in an amount of more than 6 wt% of the dry weight of the composition. This refers to the uncoated composition or the core. The surfactant may comprise more than 12 wt% of the oil phase, for example in the liquid composition. The surfactant may be present in the composition in an amount of from about 5% to about 20%, from about 8% to about 20%, from about 8% to about 15%, or from about 10% to about 14% by weight based upon the dry weight of the core. It is to be understood that reference to the "dry weight of the core" means the weight of the components present in the uncoated core other than water.

[0049] The weight ratio of the surfactant : oil may be from about 5:1 to about 1:5, from about 3:1 to about 1:2, from about 3:1 to about 1:1 or from about 2.5:1 to 1.5:1. Suitably the weight ratio may be about 1:1, about 2:1, about 2.5:1, about 3:1, about 1:1.5 or about 1:2.

[0050] Accordingly, in a preferred example there is provided a liquid composition comprising an aqueous phase, a surfactant and an oil phase in which cyclosporin is dissolved, wherein the aqueous phase comprises a hydrogel forming polymer, the oil phase is dispersed in the aqueous phase and the surfactant comprises or is a surfactant selected from: glyceryl caprylate/caprate (Capmul MCM), glyceryl monooleate/dioleate (Capmul GMO-50), glycerol monolinoleate (Maisine 35-1) and a combination thereof. The oil phase may be dispersed in the aqueous phase in the form of a colloid, for example a liquid-liquid colloid. The oil phase may be dispersed in the aqueous phase in the form of an emulsion. Accordingly, the liquid composition may be a liquid emulsion composition.

[0051] There is provided a composition comprising cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix, wherein the surfactant comprises or is a surfactant selected from: glyceryl caprylate/caprate (Capmul MCM), glyceryl monooleate/dioleate (Capmul GMO-50), glycerol monolinoleate (Maisine 35-1) and a combination thereof. The composition may be a solid composition. The composition may be in the form of a dried bead. The composition may be in the form of a dried colloid.

[0052] Optionally, the surfactant is or comprises glyceryl monooleate, glyceryl dioleate or a combination thereof. Capmul GMO -50 is an example of a commercially available surfactant that comprises a combination of glyceryl monooleate and glyceryl dioleate. Thus, the surfactant may be Capmul GMO-50. Where Capmul GMO-50 is mentioned in the specification it will be understood that it is referring to a mixture of glyceryl monooleate and glyceryl dioleate. Capmul GMO-50 may also refer to glyceryl monooleate alone.

[0053] Similarly, the skilled person would understand that a surfactant that is described as, for example glyceryl monooleate/dioleate, contemplates a combination of glyceryl monooleate and glyceryl dioleate. In other words a "/" in a surfactant name indicates that the surfactant is a mixture of two components.

[0054] The composition may comprise a coating to control or modulate release of the cyclosporin from the composition. Advantageously the coating is a polymeric coating to provide delayed and/or sustained release of the cyclosporin from the composition. Suitably such coatings are described in more detail below and include a coating which is or comprises a coating selected from a controlled release polymer, a sustained release polymer, an enteric polymer, a pH independent polymer, a pH dependent polymer and a polymer specifically susceptible to degradation by bacterial enzymes in the gastrointestinal tract, or a combination of two or more such polymers. In a particular example the coating is or comprises a pH-independent polymer, for example a coating which is or comprises ethyl cellulose. In a further specific example the coating is or comprises a pH-independent polymer, for example ethyl cellulose, and optionally a water-soluble polysaccharide, for example pectin or chitosan, or a combination thereof, particularly pectin.

[0055] In an example the coating that is referred to in the preceding paragraph is an outer coating, also referred to as a second coating. The composition may optionally comprise a further coating, referred to as a sub-coat or a first coating. The respective polymers of the first coating and the second coating are different. Often the second coating does not have any polymer found in the first coating; for example, if the first coating comprises (e.g. is) a hydroxypropylmethyl cellulose, then the second coating will not also comprise a hydroxypropylmethyl cellulose. In addition the situation is contemplated where the first coating is or comprises a water-soluble ether or ester of a cellulose ether, the major component(s) (e.g. more than 50%) of the second coating is or comprises a different polymer to that of the first coating. Accordingly, the first and second coatings suitably provide two layers of material as part of the composition. It is to be understood that when the second coating comprises a mixture of components, minor components of the outer second coating may be the same as the material of the sub-coating. By way of example, when the first coating is or comprises HPMC and the second coating comprises ethyl cellulose, the ethyl cellulose may optionally further comprise a minor amount (e.g. less than 50%,40%, 30% or 20%) of the first coating material, HPMC in this example. In such examples the first coating and the second coating are considered to be different.

[0056] The composition of the disclosure may comprise cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix, wherein the surfactant may be a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and may not comprise or may not be a polyethyleneglycol ether or ester. Optionally, the composition may further comprise a first coating, wherein the first coating is or comprises a water-soluble cellulose ether as described above and elsewhere herein. In addition to the first coating or alternatively to the first coating the composition may comprise a second coating. Optionally, the second coating is or comprises a coating, suitably a polymeric coating, to control or modulate release of the active ingredient from the composition. The polymeric coating may be as further described elsewhere in this specification.

[0057] Where the composition comprises a first coating and a second coating the second coating may be outside the first coating.

[0058] The composition may comprise: a core, wherein the core comprises cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix; a first coating outside the core, wherein the first coating is a water-soluble cellulose ether as described above and elsewhere herein; and a second coating outside the first coating, wherein the surfactant is as described herein, the surfactant being, for example, a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and not comprising or not being a polyethyleneglycol ether or ester. Throughout this specification "core" may refer to a core comprising cyclosporin, a hydrogel forming polymer matrix, a surfactant, as described herein, and an oil phase being dispersed in the hydrogel forming polymer matrix.

[0059] According to an example of the disclosure, the surfactant optionally is a medium chain or long chain fatty acid mono-glyceride, di-glyceride or a combination thereof, the first coating is or comprises a water-soluble cellulose ether, and the composition further comprises a second coating

outside the first coating wherein the second coating is or comprises a coating, suitably a polymeric coating, to control or modulate release of the active ingredient from the composition. The polymeric coating may be as further described elsewhere in this specification.

[0060] The first coating suitably may be or comprise a water-soluble cellulose ether. The water-soluble cellulose ether may be any cellulose ether or derivative of a cellulose ether, for example an ester of a cellulose ether that is soluble in water. Therefore, the water-soluble cellulose ether may be selected from: an alkyl cellulose; a hydroxyalkyl cellulose; a hydroxyalkyl alkyl cellulose; and a carboxyalkyl cellulose. Suitably the first coating is or comprises one or more water-soluble cellulose ethers selected from: methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose, and combinations thereof. In particular examples the first coating is or comprises a water-soluble hydroxypropyl methylcellulose. The water-soluble cellulose ethers and water-soluble derivatives thereof (e.g. water-soluble esters of a cellulose ether) present in the first coating (sub-coat) suitably form at least 20%, 40%, 50%,60%, 70%, 80%, 85% or 90% by weight of the dry weight of the first coating.

[0061] In accordance with the present disclosure there is provided a pharmaceutical composition comprising a core and a first coating, wherein the core comprises cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix and the first coating comprises or is a water soluble cellulose ether and the first coating is present in an amount corresponding to a weight gain due to the first coating of from 0.5% to 20% by weight of the core, wherein the surfactant is as described herein, for example a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and not comprising or not being a polyethyleneglycol ether or ester.

[0062] The first coating of the present disclosure modifies the release of the active ingredient from the composition. There would be an expectation that a coating on a composition would slow the rate of release of the active ingredient within a composition. One might reasonably expect this as coating the composition with additional material would provide an additional barrier to a dissolution medium coming into contact with the active ingredient in the composition. In contrast to this expected outcome, the compositions of the present disclosure comprise a coating comprising or being a water soluble cellulose ether that increases the rate of release of the active ingredient compared to a composition without the coating. In addition the coating of the present disclosure has the beneficial effect of maintaining the active ingredient in solution, whereas a comparable composition lacking the coating of the disclosure provides less of the active ingredient in solution as time progresses. Without wishing to be bound by theory, it is believed that the coating prevents precipitation of the active ingredient from solution, thereby maintaining a higher amount of the active in solution.

[0063] Throughout the present application active ingredient, active, and pharmaceutically active ingredient are used interchangeably and all refer to cyclosporin, preferably cyclosporin A.

[0064] The composition of the present disclosure may take any form known to the person skilled in the art. Preferably, the composition is an oral composition. The composition may be in the form of a single minibead or a multiplicity of minibeads. Accordingly the disclosure provides a minibead

comprising cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix, wherein the surfactant is or comprises a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethyleneglycol ether or ester. The disclosure also provides a composition comprising a multiplicity of minibeads. Similarly, the disclosure provides a multiple minibead formulation comprising a unit dosage form comprising a multiplicity of minibeads.

[0065] The disclosure also provides for a pharmaceutical composition comprising a core and a first coating, wherein the core comprises cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix and the first coating comprises or is a water-soluble cellulose ether and the first coating has a thickness of from 1 μm to 1 mm wherein the surfactant is as described herein, for example a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and not comprising or not being a polyethyleneglycol ether or ester.

[0066] Any of the pharmaceutical compositions of the disclosure may comprise a further coating, referred to herein as a second coating. The second coating may be outside the first coating. The second coating may be or comprise a delayed release polymer. In any example and any example of the disclosure the first and second coating may be different.

[0067] The disclosure therefore, contemplates a pharmaceutical composition comprising a core, a first coating and a second coating outside of the first coating, wherein the core comprises cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix, the first coating comprises or is a water soluble cellulose ether (for example HPMC), and the second coating comprises or is a delayed release polymer (for example ethylcellulose), wherein the surfactant is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethyleneglycol ether or ester.

[0068] The composition of any aspect or example of the disclosure may be in the form of a solid colloid. Furthermore, the core of a composition may be in the form of a solid colloid. The colloid comprises a continuous phase and a disperse phase. Suitable continuous phases and disperse phases which may be used to form the core are defined in more detail below and in the detailed description of the disclosure. The continuous phase may comprise or be the hydrogel forming polymer matrix. Hence, where the continuous phase is the hydrogel forming polymer matrix, the composition of the disclosure may take the form of a solid unit of the hydrogel forming polymer comprising a disperse phase. The disperse phase may be droplets dispersed in the continuous phase, or the hydrogel forming polymer matrix. The disperse phase may comprise or be the oil phase.

[0069] Thus, the disclosure provides a composition in the form of a solid colloid comprising a continuous phase and a dispersed phase, wherein the continuous phase comprises or is a hydrogel forming polymer matrix and the continuous phase is or comprises oil phase, wherein the composition further comprises cyclosporin and a surfactant. Preferably, the surfactant is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethyleneglycol ether or ester. The oil phase may comprise the cyclosporin in solution.

[0070] The composition may comprise a core in the form of a solid colloid comprising a continuous phase and a dispersed phase, wherein the continuous phase comprises or is a hydrogel forming polymer matrix and the continuous phase is or comprises oil phase, wherein the core further comprises cyclosporin and a surfactant, wherein the surfactant is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethyleneglycol ether or ester. The oil phase may comprise the cyclosporin in solution.

[0071] The continuous phase of a solid colloid composition or core is or comprises a hydrogel-forming polymer matrix. In examples the hydrogel-forming polymer matrix is or comprises a hydrocolloid, a non-hydrocolloid gum or chitosan. In a particular example the hydrogel-forming polymer matrix is or comprises gelatin, agar, a polyethylene glycol, 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 and polyvinylacetate-phthalate and any derivative of any of the foregoing; or a mixture of two or more such polymers. In a further example the hydrogel-forming polymer matrix is or comprises a hydrocolloid selected from carrageenan, gelatin, agar and pectin, or a combination thereof optionally selected from gelatin and agar or a combination thereof. Particularly, the polymer of the hydrogel-forming polymer matrix is or comprises gelatin. In an example, the hydrogel-forming polymer does not comprise a cellulose or a cellulose derivative, e.g. does not comprise a cellulose ether.

[0072] Also disclosed is the composition may be in the form of a solid colloid the colloid comprising a continuous phase and a disperse phase and the cyclosporin may be in solution or suspended in the disperse phase. For example, the cyclosporin may be in solution in the disperse phase.

[0073] It is to be understood that the individual examples described above may be combined with one or more of the other examples described to provide further examples of the disclosure.

[0074] The first coating may be in contact with the core. The second coating may be on the first coating. In examples the first coating is in contact with the core and the second coating is on the first coating.

[0075] The second coating may be or may comprise a delayed release polymer and the delayed release polymer may be selected from an enteric polymer, a pH independent polymer, a pH dependent polymer and a polymer specifically susceptible to degradation by bacterial enzymes in the gastrointestinal tract, or a combination of two or more such polymers. Hence, the second coating may be any of the aforementioned delayed release polymers or any may be or possess the characteristics mentioned in relation to the delayed release polymer mentioned below.

[0076] In examples the delayed release polymer may be water-soluble or water-permeable in an aqueous medium with a pH greater than 6.5. The delayed release polymer may be or comprise a pH-independent polymer, for example ethyl cellulose.

[0077] In any aspect and any example of the disclosure the water-soluble cellulose ether may be selected from any one or a combination of: methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose. The water-soluble cellulose ether may preferably be hydroxylpropyl methylcellulose (HPMC).

[0078] In examples the first coating may be or comprise hydroxypropyl methyl cellulose and the second coating may be or comprise ethyl cellulose.

[0079] The disclosure of the weight gain of the first coating is given as a % by weight of the core. Similarly, the weight gain of the second coating is given as a % by weight of the core, where there is no first coating (sub-coat) on the core. Where the composition comprises a first coating, the weight gain of the second coating is given as a % by weight of the composition that is coated by the second coating, for example the core and the first coating.

[0080] The hydrogel forming polymer or the hydrogel forming polymer matrix may be or comprise a hydrocolloid, a non-hydrocolloid gum or chitosan. The hydrogel forming polymer or the hydrogel forming polymer matrix may be a reversible hydrocolloid, for example a thermoreversible hydrocolloid or a thermoreversible hydrogel forming polymer. Alternatively, the hydrogel forming polymer or the hydrogel forming polymer matrix may be or comprise an irreversible hydrocolloid. The hydrogel forming polymer or the hydrogel forming polymer matrix may be or comprise gelatin, agar, a polyethylene glycol, 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 and polyvinylacetate-phthalate and any derivative of any of the foregoing; or a mixture of one or more such a hydrogel forming polymers. The hydrogel forming polymer or the hydrogel forming polymer matrix may be or comprise 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 hydrogel forming polymer or the or the hydrogel forming polymer matrix forming polymer matrix is or comprises gelatin. The hydrogel forming polymer matrix is or comprises a non-hydrocolloid gum optionally selected from a cross-linked salt of alginic acid. In preferred examples the hydrogel forming polymer or the hydrogel forming polymer matrix is or comprises gelatin.

[0081] In examples the hydrogel forming polymer or the hydrogel forming polymer matrix further comprising a plasticiser, optionally a plasticiser selected from glycerin, a polyol for example sorbitol, polyethylene glycol and triethyl citrate or a mixture thereof, particularly sorbitol.

[0082] The hydrogel forming polymer matrix may encapsulate the cyclosporin. The cyclosporin may be encapsulated in solution. The cyclosporin may be in solution or suspended in another component, for example the oil phase or the disperse phase discussed elsewhere, of the composition that is also encapsulated by the hydrogel forming polymer matrix.

[0083] The disperse phase may be solid, semi-solid or liquid. In particular, the disperse phase may be liquid. In other particular instances the disperse phase may be semi-solid, for example it may be waxy.

[0084] The disperse phase may be or comprise the oil phase, for example the oil phase may be a solid, a semi-solid or a liquid. Suitably the disperse phase or the oil phase is or comprises a liquid lipid and optionally a solvent miscible therewith. The liquid lipid is optionally a medium chain mono- di- or triglyceride (particularly a medium chain triglyceride).

[0085] Suitably, cyclosporin is soluble in the solvent. The solvent may be an alcohol (for example ethanol or isopropanol), a glycol (for example propylene glycol or a polyethylene glycol) or a glycol ether. The solvent may be a glycol ether, for example an ethylene glycol ether, more particularly an alkyl, aryl or aralkyl ethylene glycol ether. The solvent may be a glycol ether selected from 2-methoxyethanol; 2-ethoxyethanol; 2-propoxyethanol; 2-isopropoxyethanol; 2-butoxyethanol; 2-phenoxyethanol; 2-benzyloxyethanol; 2-(2-methoxyethoxy)ethanol; 2-(2-ethoxyethoxy)ethanol; and 2-(2-butoxyethoxy)ethanol. More particularly the solvent is 2-(2-ethoxyethoxy)ethanol or 2-phenoxyethanol. A particular solvent is 2-(2-ethoxyethoxy)ethanol.

[0086] The cyclosporin may be dissolved in the disperse phase. The cyclosporin may be suspended in the disperse phase. The disperse phase may be as described elsewhere herein, for example it may be as described in the immediately preceding two paragraphs.

[0087] The oil phase or disperse phase may be or may comprise a liquid lipid. Particularly, the oil phase or disperse phase may comprise or be a short-, medium- or long- chain triglyceride formulation, or a combination thereof, for example a caprylic/capric triglyceride, i.e. a caprylic/capric triglyceride formulation.

[0088] Accordingly, in an example the liquid composition comprises an aqueous phase, a surfactant and an oil phase in which cyclosporin is dissolved, wherein the surfactant may comprise or be a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise is not a polyethyleneglycol ether or ester, the aqueous phase may comprise a hydrogel forming polymer, and the oil phase comprises a short-, medium- or long- chain triglyceride formulation, or a combination thereof (optionally a caprylic/capric triglyceride, i.e. a caprylic/capric triglyceride formulation) and is dispersed in the aqueous phase. The oil phase may be dispersed in the aqueous phase in the form of a colloid, for example a liquid-liquid colloid. The oil phase may be dispersed in the aqueous phase in the form of an emulsion. Accordingly, the liquid composition may be a liquid emulsion composition.

[0089] Additionally, in an example the composition comprises cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase comprising a short-, medium- or long- chain triglyceride formulation, or a combination thereof (optionally a caprylic/capric triglyceride, i.e. a caprylic/capric triglyceride formulation) and being dispersed in the hydrogel forming polymer matrix, wherein the surfactant may be or may comprise a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethyleneglycol ether or ester. The composition may be in the form of a dried colloid. The composition may be in the form of a bead.

[0090] In a particular example the disperse phase or the oil phase further comprises a solvent, thus optionally the disperse phase or the oil phase may be or comprise a liquid lipid and a solvent. The

solvent may be miscible with the liquid lipid 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. In a further example the disperse phase or oil phase is or comprises a medium chain mono- di- or triglyceride (particularly a medium chain triglyceride), 2-(ethoxyethoxy)ethanol and the surfactant. The disperse phase or oil phase as described in this paragraph may contain the cyclosporin, the cyclosporin may optionally be in solution.

[0091] Preferably, the oil phase or disperse phase comprises a short-, medium- or long- chain triglyceride formulation, or a combination thereof (optionally a caprylic/capric triglyceride, i.e. a caprylic/capric triglyceride formulation). Where the oil phase or disperse phase comprises a short-, medium- or long- chain triglyceride formulation, or a combination thereof, the triglyceride is substantially all of the disperse phase or oil phase (optionally the liquid lipid). For example, the oil phase or disperse phase may comprise short-, medium- or long- chain triglyceride formulation in an amount of greater than 80% of the oil phase or disperse phase (optionally the liquid lipid), optionally greater than 85%, 90%, 95%, 97%, 98% or 99%. Suitably, the short-, medium- or long- chain triglyceride formulation is substantially free of mono- or di-glycerides. For example, the surfactant may comprise less than 10%, 8%, 5%, 3%, 2% or 1% of a mono- or di-glycerides.

[0092] In examples the composition further comprises one or more additional surfactants, preferably one additional surfactant. The additional surfactant may be referred to as a second surfactant or further surfactant throughout the specification and these terms are used interchangeably. Where the compositions of the disclosure comprise a second surfactant the surfactant that may be or may comprise a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethyleneglycol ether or ester is referred to as a first surfactant.

[0093] Suitable surfactants for the second surfactant are described in more detail in the detailed description of the disclosure. The second surfactant may be an anionic or non-ionic surfactant. The second surfactant may be a sucrose monoester, an alkyl sulfate or a polyethylene glycol alkyl ether. The second surfactant may be sucrose laurate, sucrose palmitate, sodium octyl sulfate, sodium octadecyl sulfate, sodium dodecyl sulphate, polyethylene glycol hexadecyl ether, polyoxyethylene glycol octadecyl ether, or polyethylene glycol dodecyl ether. Optionally, the second surfactant may be sodium octyl sulfate, sodium octadecyl sulfate, sodium dodecyl sulphate or polyethylene glycol dodecyl ether.

[0094] Preferably the second surfactant is an anionic surfactant. For example, the second surfactant may be an alkyl sulphate, for example sodium octyl sulfate, sodium octadecyl sulfate, or sodium dodecyl sulphate (preferably sodium dodecyl sulphate).

[0095] In those examples where the liquid composition is in the form of a colloid, the composition is in the form of a solid colloid or the composition comprises a core in the form of a solid colloid, the colloid comprises a continuous phase and a disperse phase, wherein the continuous phase comprises the hydrogel-forming polymer matrix and the second surfactant may be present in the continuous phase, the disperse phase or both. Preferably the second surfactant is present in the continuous phase and the first surfactant is present in the disperse phase. Accordingly, the aqueous

phase of the liquid composition may comprise the second surfactant and the oil phase may comprise the first surfactant. In one example the core further comprises one additional surfactant present in at least the continuous phase, the surfactant having an HLB value of greater than 10, for example greater than 20.

[0096] The composition may have the characteristics of a composition formed by mixing a disperse phase with a continuous phase to form a colloid, wherein the continuous phase is an aqueous phase comprising hydrogel forming polymer and the disperse phase is a oil phase, wherein the pharmaceutically active ingredient is in the continuous phase or the disperse phase, wherein the colloid is gelled to form the composition. The composition is thus in the form of a solid colloid.

[0097] Furthermore, the composition may comprise a core having the characteristics of a core formed by mixing a disperse phase with a continuous phase to form a colloid, wherein the continuous phase is an aqueous phase comprising hydrogel forming polymer and the disperse phase is a oil phase, wherein the pharmaceutically active ingredient is in the continuous phase or the disperse phase, wherein the colloid is gelled to form the core. The core is thus in the form of a solid colloid.

[0098] The cyclosporin may be present in the composition in solution or in suspension. In the example where the disclosure provides a liquid composition the cyclosporin is in solution.

[0099] The liquid composition comprises an aqueous phase, a surfactant and an oil phase in which cyclosporin is dissolved and may have the characteristics of a liquid composition obtained by a process comprising:

(i) dissolving a hydrogel-forming polymer in an aqueous liquid to form an aqueous phase solution;

(ii) dissolving the cyclosporin in the oil phase to form a solution; and

(iii) mixing the aqueous phase solution (i) and the oil phase solution (ii) to form a colloid (optionally an emulsion).

[00100] The composition or core of the disclosure may have the characteristics of a composition obtained by a process comprising:

(a) ejecting the liquid composition through a nozzle to form droplets;

(b) causing or allowing the a hydrogel-forming polymer to gel or solidify to form a hydrogel-forming polymer matrix; and

(c) drying the solid.

[00101] The composition or core comprises cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase and may have the characteristics of a composition obtained by a process comprising:

(i) dissolving a hydrogel-forming polymer in an aqueous liquid to form an aqueous phase solution;

(ii) dissolving the cyclosporin in the oil phase to form a solution;

(iii) mixing the aqueous phase solution (i) and the oil phase solution (ii) to form a colloid (optionally an emulsion);

(iv) ejecting the colloid through a nozzle to form droplets;

(v) causing or allowing the a hydrogel-forming polymer to gel or solidify to form a hydrogel-forming polymer matrix; and

(vi) drying the solid.

[00102] The aqueous phase and oil phase may be mixed (for example in step (iii)) in an oil phase to aqueous phase ratio of from 1:4 to 1:10, optionally from 1:4 to 1:8, from 1:5 to 1:7. For example, the oil phase to aqueous phase ratio may be 1:4, 1:5, 1:6 or 1:7.

[00103] The oil phase solution (ii) may be prepared by dissolving or dispersing the cyclosporin A in a suitable hydrophobic liquid. The hydrophobic liquid may be for example, any of the oils or liquid lipids described herein. By way of example the hydrophobic liquid may be, or comprise, saturated or unsaturated fatty acids or a triglyceride, or an ester or ether thereof with polyethylene glycols. A particular oil for the oil phase is or comprises a triglyceride, for example an oil comprising a medium chain triglyceride, optionally wherein the oil comprises a triglyceride of at least one fatty acid selected from fatty acids having 6, 7, 8, 9, 10, 11 or 12 carbon atoms, e.g. C_8-C_{10} fatty acids.

[00104] The aqueous phase solution (i) may further comprise a surfactant selected from: sucrose monoester, an alkyl sulfate and a polyethylene glycol alkyl ether, optionally the sselected from: sucrose laurate, sucrose palmitate, sodium octyl sulfate, sodium octadecyl sulfate, sodium dodecyl sulphate, polyethylene glycol hexadecyl ether, polyoxyethylene glycol octadecyl ether, and polyethylene glycol dodecyl ether. The aqueous phase solution (i) may further comprise a surfactant selected from: sodium octyl sulfate, sodium octadecyl sulfate, sodium dodecyl sulphate or polyethylene glycol dodecyl ether. Preferably, the aqueous phase solution (i) further comprises an anionic surfactant, e.g. as described elsewhere herein, for example sodium dodecyl sulphate (SDS).

[00105] In one example the liquid composition or composition having the characteristics of a liquid composition or composition obtained by the process above is a composition or liquid composition comprising an oil phase dispersed in the aqueous phase solution, wherein the liquid composition or composition is or comprises cyclosporin, glyceryl monooleate/dioleate, gelatin, SDS, sorbitol, caprylic/capric triglyceride, 2-(ethoxyethoxy)ethanol; wherein the aqueous phase solution (i) is or comprises gelatin, sorbitol and SDS; and the oil phase solution (ii) is or comprises cyclosporin, glyceryl monooleate/dioleate, caprylic/capric triglyceride, 2-(ethoxyethoxy)ethanol and the active ingredient.

[00106] Cores having the characteristics of cores obtained by the above-described processes, for example cores obtained by the processes, may be coated to provide a coating that comprises or is a water-soluble cellulose ether, optionally with a second coating to control or modify release, preferably a polymeric coating as described above and herein. The coated composition may be obtained by applying to the core the coating, e.g. applying to the core first and second coatings as described. Before the coating is applied, the core may be made by a process having steps (i) to (vi) or (i) to (v) described above. Suitable methods for applying the coating(s) are described below and include applying the coatings by spray coating a coating composition onto the core. The processes having steps (i) to (vi) or (i) to (v) themselves form examples of the disclosure.

[00107] The composition or core may further comprise a second surfactant (also referred to as a further surfactant), optionally wherein the second surfactant is an anionic surfactant, optionally selected from alkyl sulphates, carboxylates or phospholipids, or a non-ionic surfactant, optionally selected from sorbitan-based surfactants, PEG-fatty acids, fatty alcohol ethoxylates, alkylphenol ethoxylate, fatty acid ethoxylates, fatty amide ethoxylates, alkyl glucosides or glyceryl fatty acids, or poloxamers, or a combination thereof. Hence the liquid composition of the disclosure may comprise at least the following features, an aqueous phase comprising a hydrogel forming polymer, a first surfactant and an oil phase being dispersed in the aqueous phase in which cyclosporin is dissolved and a second surfactant. Similarly, the composition of the disclosure may comprise at least the following features, cyclosporin, a hydrogel forming polymer matrix, a first surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix and a second surfactant.

[00108] In examples where the composition is in the form of a solid colloid, the second surfactant may be in the disperse phase or the continuous phase. The second surfactant may be in the continuous phase and may be an anionic surfactant, for example at least one surfactant selected from fatty acid salts and bile salts, particularly an alkyl sulphate, for example sodium dodecyl sulphate. The surfactant in the disperse phase may be a non-ionic surfactant.

[00109] In examples the composition comprises a second surfactant which is or comprises an anionic surfactant, for example sodium dodecyl sulphate, which is in the continuous phase.

[00110] In examples the composition further comprises a combination of excipients selected from: an anionic surfactant and a solvent; an anionic surfactant and an oil; and an anionic surfactant, a solvent and an oil. Preferably, the anionic surfactant is an alkyl sulphate, for example sodium dodecyl sulphate, the oil is a medium chain mono-, di- and/or tri-glyceride (optionally a medium chain triglyceride, for example caprylic/capric triglyceride, and the solvent is 2-(ethoxyethoxy)ethanol.

[00111] The composition may further comprise an excipient selected from: a surfactant, a solubiliser, a permeability enhancer, a disintegrant, a crystallisation inhibitor, a pH modifier, a stabiliser, or a combination thereof.

[00112] The composition of the disclosure or, where the composition comprises a core, the core may comprise a disperse phase or oil phase, wherein the disperse phase or oil phase is or comprises:

cyclosporin;

a medium or long chain fatty acid mono- or di-ester or a combination thereof which does not comprise is not a polyethyleneglycol ether or ester, such as a medium or long chain fatty acid mono- or di-glyceride or a combination thereof, for example glyceryl monooleate/dioleate;

a medium chain mono- di- or tri-glyceride, for example caprylic/capric triglyceride; and

a solvent, for example 2-(ethoxyethoxy)ethanol

and the composition or the core may further comprise a continuous phase or aqueous phase being or comprising:

an anionic surfactant, for example at least one surfactant selected from fatty acid salts and bile salts, particularly an alkyl sulphate, for example sodium dodecyl sulphate

a hydrogel forming polymer matrix which is or 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 a hydrogel forming polymer matrix is or comprises gelatin; and

optionally a plasticiser, for example a plasticiser selected from glycerin, a polyol for example sorbitol, polyethylene glycol and triethyl citrate or a mixture thereof, particularly sorbitol.

[00113] In one example the composition comprises a core and a coating outside the core, wherein the core is in the form of a solid colloid, the colloid comprising a continuous phase and a disperse phase, wherein the disperse phase is or comprises:

cyclosporin A;

a medium or long chain fatty acid mono- or di-glyceride or a combination thereof which does not comprise is not a polyethyleneglycol ether or ester, for example glyceryl monooleate/dioleate;

a medium chain mono- di- and/or tri-glyceride, for example caprylic/capric triglyceride; and

a co-solvent, for example 2-(ethoxyethoxy)ethanol;

and wherein the continuous phase is or comprises:

a hydrogel-forming polymer matrix which is or 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 water-soluble polymer matrix is or comprises gelatin;

optionally a plasticiser, optionally a plasticiser selected from glycerin, a polyol for example sorbitol, polyethylene glycol and triethyl citrate or a mixture thereof, particularly sorbitol; and

an anionic surfactant, for example at least one surfactant selected from fatty acid salts and bile salts, particularly an alkyl sulphate, for example sodium dodecyl sulphate;

and wherein the coating on the core is a first coating or a second coating, as described herein.

[00114] Suitably the coating comprises a first coating and a second coating outside the first coating; and wherein

the first coating is the coating which is or comprises a water-soluble cellulose ether as described above; and

the second coating is or comprises a coating, suitably a polymeric coating, as defined above to control or modulate release of cyclosporin A from the composition.

[00115] In examples comprising a first coating and/or a second coating, for example as mentioned in the immediately preceding paragraph, a particular first coating is or comprises hydroxypropylmethyl cellulose and a particular second coating outside the first coating is or comprises a pH independent polymer, for example ethyl cellulose; more particularly the second coating is or comprises ethyl cellulose and optionally a polysaccharide selected from water soluble and naturally occurring polysaccharides, for example pectin or another water-soluble naturally occurring polysaccharide. The second coating may therefore contain pectin or another said polysaccharide or it may be substantially free of pectin and other said polysaccharides. There are therefore disclosed second coatings which comprise ethylcellulose as a controlled release polymer and which further comprise pectin or another said polysaccharide as well as second coatings which comprise

glyceryl monooleate and/or glyceryl dioleate in an amount of 100 – 150 mg/g; and

SDS in an amount of 15 – 60 mg/g or 15 – 50 mg/g (optionally 25 – 50 mg/g or 25 – 45 mg/g); and

optionally D-sorbitol in an amount of 30 – 80 mg/g.

[00121] The composition or the core may comprise:

gelatin in an amount of 380 – 500 mg/g;

cyclosporin in an amount of 90 – 140 mg/g; and

caprylic/capric triglyceride in an amount of 40 – 80 mg/g;

2-(2-ethoxyethoxy) ethanol in an amount of 160 – 200 mg/g;

glyceryl monooleate and/or glyceryl dioleate in an amount of 100 – 150 mg/g; and

SDS in an amount of 15 – 50 mg/g (optionally 25 – 50 mg/g or 25 – 45 mg/g); and

optionally D-sorbitol in an amount of 30 – 80 mg/g.

[00122] The composition or core may be a colloid. Where the composition or the core is a colloid, the cyclosporin may be dissolved in the disperse phase of the colloid.

[00123] The composition or core may be a colloid; thus, the composition or core may comprise a continuous phase and a disperse phase wherein the continuous phase comprises:

gelatin in an amount of 380 – 500 mg/g; and

optionally D-sorbitol in an amount of 30 – 80 mg/g;

the disperse phase comprises:

cyclosporin in an amount of 90 – 140 mg/g; and

caprylic/capric triglyceride in an amount of 40 – 80 mg/g;

and the composition further comprises:

2-(2-ethoxyethoxy)ethanol in an amount of 160 – 200 mg/g;

glyceryl monooleate and/or glyceryl dioleate in an amount of 100 – 150 mg/g; and

SDS in an amount of 15 – 50 mg/g.

[00124] A colloidal composition or core 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 (a first surfactant) being or comprising a medium or long chain fatty acid mono- or di-ester or a combination thereof which does not comprise is not a polyethyleneglycol ether or ester, for example glyceryl monooleate/dioleate; and

anionic surfactant (a second surfactant) in an amount of up to 50 mg/g.

[00125] In the examples above which refer to mg/g of a component, the concentration is based upon the dry weight of the composition.

[00126] Suitably in the six compositions or cores described immediately above, the composition is a colloid comprising a disperse phase and a continuous phase; wherein the disperse phase comprises cyclosporin, medium-chain triglyceride and medium or long chain fatty acid mono- or di-ester surfactant; and the continuous phase comprises the hydrogel forming polymer (e.g. gelatin) and an anionic surfactant (e.g. SDS).

[00127] The disclosure includes within its scope compositions wherein the core is a colloid having a disperse phase and the continuous phase (matrix phase) of the colloid further includes dispersed particles of a pharmaceutically active ingredient, for example microparticles or nanoparticles. The disperse phase and continuous phase may otherwise be as described elsewhere in this specification.

[00128] The composition of the disclosure and / or the core may be in the form of a minibead. It may be that the core is a minibead and the first coating and, where applicable, the second coating in conjunction with the core are in the form of a minibead. However, it may be possible for the core to be a minibead and the composition not to be a minibead. The composition may additionally comprise a multiplicity of minibeads. Hence the disclosure contemplates a minibead with the features of the pharmaceutical compositions disclosed herein.

[00129] The composition or the minibead may have a largest cross sectional dimension of a core of from about 0.01 mm to about 5 mm, for example from 1 mm to 5 mm, as in the case of from 1mm to 3mm or 1mm to 2mm. The minibead may be spheroidal. The spheroidal minibeads may have an aspect ratio of no more than 1.5, for example from 1.1 to 1.5.

[00130] The composition of the disclosure may be for oral administration. The composition may be formulated into a unit dosage form for oral administration comprising from 0.1 mg to 1000 mg, optionally from 1mg to 500 mg, for example 10mg to 300 mg, or 25 to 250 mg suitably about 25mg, about 35 mg, about 37.5 mg, about 75mg, about 150 mg, about 180 mg, about 210 mg, about 250 mg or about 300 mg of cyclosporin. Suitably the composition is in a multiple minibead unit dosage form selected from multiple minibeads in, for example, soft or hard gel capsules, gelatin capsules, HPMC capsules, compressed tablets or sachets. The minibeads may be as described elsewhere herein.

[00131] The compositions described herein may be used to deliver cyclosporin A locally to specific locations in the GIT, for example the solid compositions described herein, may be adapted to provide release of cyclosporin A in at least the colon. The compositions may be used to provide the cyclosporin A locally in the GIT in a solubilised form, thereby providing high concentrations of cyclosporin in an active (available) form within the GIT where it acts to provide a therapeutic benefit in a number of medical conditions, particularly conditions affecting the GIT as described in more detail herein, such as ulcerative colitis. The release of cyclosporin A in an active form, for example a solubilised form, enables high concentrations of cyclosporin A to be absorbed directly into the local tissues of the GIT, such as the colon. However, as described above, systemic exposure cyclosporin A has a number of undesirable side effects. Therefore, a cyclosporin A composition which minimises systemic exposure to cyclosporin whilst maintaining therapeutically beneficial concentrations in the tissues of the GIT would be desirable.

[00132] The major pathways of cyclosporin A metabolism in humans are via cytochrome P450 3A4 (CYP 3A4) and cytochrome P450 2J2 (CYP 2J2), with three major metabolites being formed (two hydroxylated metabolites AM1, AM9 and one N-demethylated metabolite, AM4N). These metabolites have minimal, if any immunosuppressive activity. Therefore minimising the metabolism of cyclosporin is desirable, because this minimises the formation of inactive metabolites and maximises the quantity of cyclosporin available to interact locally with the tissues in the GIT. The primary metabolism of cyclosporin is via CYP 3A4, which is mainly found in the liver and the small intestine.

[00133] The total mass of CYP3A in the entire small intestine has been estimated to be_1% of that in the liver. However, despite the relatively low mass of CYP3A in the small intestine, enteric CYP3A can contribute significantly, and in some cases equally, with hepatic CYP3A, to the overall first-pass metabolism of several drugs including cyclosporin (Paine et al; Drug Metabolism and Disposition, Vol 34(5), 2006, 880-885). CYP 3A4 expression in the colon is lower than in the small intestine. Compositions which control the release of cyclosporin to limit or inhibit release in the upper GI tract, for example, by using one or more modified release coatings, may reduce enteric (i.e. non-systemic or "pre-systemic") P450 metabolism. However, some metabolism would still be expected resulting from the P450 expressed in the tissues in the lower GIT.

[00134] It has been found that certain compositions described herein, particularly compositions which release cyclosporin in the lower GI tract, especially in the colon, provide very low levels of cyclosporin metabolism following oral administration of the composition. The compositions therefore maximise the amount of active (solubilised) cyclosporin available to interact with the tissues of the GI tract following release of the cyclosporin from the composition. Without wishing to be bound by theory, it is thought that certain components present in the composition, for example the medium chain or long chain fatty acid mono- or di-glyceride surfactant present in the composition, may act to inhibit cyclosporin metabolism by CYP 3A4 present in the tissues of the GI tract. When the composition is provided in a modified release format which prevents or inhibits release of cyclosporin in the upper GI tract, systemic absorption and metabolism of cyclosporin in liver is also minimised. Therefore, the modified release compositions described herein minimise both systemic and enteric metabolism of cyclosporin. Low levels of cyclosporin metabolism may enable a lower dose of cyclosporin to be administered whilst maintaining a therapeutic benefit, thereby, widening the therapeutic window of the drug.

[00135] The relative degree of cyclosporin metabolism following oral administration of a composition may be assessed by, for example, measuring the concentration of cyclosporin and the concentration of cyclosporin metabolites present in a faecal sample collected from a patient following oral administration of a composition comprising cyclosporin. As will be illustrated in the Examples, modified release compositions comprising cyclosporin and the surfactant (for example Capmul GMO-50) resulted in very low levels of cyclosporin metabolism compared to a similar composition comprising a different surfactant (Cremophor). Compositions, particularly orally administered compositions, which exhibit low cyclosporin metabolism following release of cyclosporin from the composition, form a further example of the disclosure.

[00136] Accordingly, there is provided a composition comprising cyclosporin A, wherein 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. The mean concentration of cyclosporin A: the concentration of cyclosporin A metabolites in the faecal sample may be selected from: greater than 19:1; greater than 24:1; greater than 31:1 and greater than 50:1. The mean concentration of cyclosporin A: the concentration of cyclosporin A metabolites in the faecal sample may be selected from: from 20:1 to 30:1; from 20:1 to 35:1; from 20:1 to 40:1; from 20:1 to 60:1; from 30:1 to 50:1; and from 20:1 to 100:1. The mean concentration of cyclosporin A: the concentration of cyclosporin A metabolites in the faecal sample may be selected from 12.5:1 to 90:1; from 13:1 to 85:1; from 15:1 to 85:1; from 16:1 to 85:1; from 20:1 to 83:1; and from 65:1 to 79:1; optionally wherein the ratio is about 76:1.

[00137] The mean concentration of cyclosporin A: the concentration of cyclosporin A metabolites in the faecal sample may be determined from a faecal sample collected from 12 to 28 hours after oral administration of a single dose of the composition to the human. Alternatively the faecal sample may be collected after a more prolonged period of regular oral administration of the composition to the human, after which the cyclosporin and metabolite concentrations in the faeces may have reached a steady state, thereby reducing the variability in the measured ratio of cyclosporin : metabolites. For example, the faeces may be collected 4 to 6 hours after the oral administration of the last dose of a dosage regimen wherein the cyclosporin composition is orally administered once or twice per day for 2, 3 4, 5, 6 or 7 days. The faeces may, for example, be collected after oral administration of 75mg of cyclosporin once or twice per day. Suitably, the faecal sample is collected 4 to 6 hours after oral administration of the last dose of a dosing regimen of the composition; the dosing regimen comprising once or twice daily oral administration of the composition to the human for seven days; optionally wherein the dosing regimen comprises once daily administration of the composition comprising 75mg of cyclosporin A for seven days. In a further example the composition comprising cyclosporin is orally administered once per day for two days (for example as a single 75 mg daily dose of cyclosporin) and the faecal sample is collected 4 to 6 hours after the last dose of the composition on the second day.

[00138] The main metabolites of cyclosporin are the AM1, AM4N and AM9 cyclosporin metabolites. The ratio of cyclosporin : cyclosporin metabolites in the faecal sample is suitably the ratio of cyclosporin: the total concentration of AM4N and AM9 cyclosporin metabolites. The ratio of cyclosporin: cyclosporin metabolites in the faecal sample may be the ratio of cyclosporin: the total concentration ofAM1, AM4N and AM9 cyclosporin metabolites.

[00139] The concentration of cyclosporin and its metabolites in the faeces may be measured using any suitable analytical method, for example chromatography and mass spectrometry as illustrated in the Examples section.

[00140] Suitably the concentrations of cyclosporin and metabolites in the faeces are measured in faecal samples obtained from healthy male subjects so as to minimise the inter-patient variability in the measured values. The faecal samples are suitably obtained from healthy male subjects aged

between 20 and 50 years, preferably weighing between 60 and 100 kg. Suitably the ratio is the arithmetic mean of the measured ratio of cyclosporin : cyclosporin metabolites in a representative number of subjects, for example at least 4, 5, 6, 7, 8, 9 or 10 subjects. Generally at least 4 subjects would be a sufficient number to provide a representative mean ratio.

[00141] The composition comprising cyclosporin A may be any composition comprising cyclosporin A which provides a ratio of cyclosporin : cyclosporin metabolites which is greater than 12:1 (or within any of the ranges described above in relation to this example of the disclosure). The composition is suitably a composition comprising cyclosporin A, wherein the composition releases cyclosporin A in a solubilised form when the composition is placed in an aqueous dissolution medium. By "solubilised" in meant that the cyclosporin in released in an active form, for example in a dissolved form such as a solution, when the composition is placed in an aqueous dissolution medium, for example an aqueous environment encountered in the lower GIT tract, particularly in the colon, following oral administration of the composition.

[00142] The composition may be, or comprise, cyclosporin A that is partially or completely dissolved in dissolved in a lipophilic substance. The lipophilic substance may be or comprise an oil, or a surfactant in which the cyclosporin is at least partially, or preferably fully dissolved. Suitable oils and surfactants which may be used include, but are not limited to any of the the oils and surfactants described herein.

[00143] In one example the cyclosporin may be dissolved or dispersed in a low melting point lipophilic substance, suitably a substance with a melting point in the range of 30 to 70°C. Suitably the hydrophobic material is a wax like solid with a melting point in the range of 30 to 60°C, particularly suitable are lipophilic waxy material which are solid at room temperature, but which melt or soften at temperatures in the range of 30 to 50°C, or more preferably 30 to 40°C. The lipophilic material may be selected from one or more of unsaturated alcohols, hydrogenated alcohols, fatty acids, fatty acid esters, fatty acid amides, fatty acid mono- di- or triglycerides, polyethoxylated fatty acids and polyethyoxylated fatty acid esters, cholesterol derivatives and waxes. The wax may be a suitable animal or plant derived wax, for example carnauba wax or a synthetic wax such as paraffin wax. The lipophilic material may comprise a wax, a saturated ot unsaturated fatty acid (for example palmitic, stearic, myristic, lauric, laurylic, or oleic acid), or a derivative thereof for example a mono-, di-, or triglyceride or a polyethylene glycol ester thereof. The lipophilic material comprising the dissolved or dispersed cyclosporin is suitably used in the form of a particulate composition, for example as a granule composition. Suitably the lipophilic substance comprising the dissolved or dispersed cyclosporin is itself dispersed, in a suitable carrier matrix. For example, granules comprising the the lipophilic substance and dissolved or dispersed cyclosporin are dispersed in a suitable carrier matrix. The carrier matrix may be a modified release matrix material, particularly a modified release polymer matrix. A modified release matrix may provide delayed or sustained release of the cyclosporin from the matrix, thereby providing a modified release composition. The carrier matrix is suitably a hydrophilic material. The matrix material may be, or comprise, acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches, starch derivatives, or natural or synthetic gums for example an alginate.

The carrier matrix may be a hydrogel forming polymer such as those described herein, including gelatin.

[00144] The composition may comprise cyclosporin A and a surfactant. Suitably the surfactant is or comprises a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof as described herein. Suitably, the in this example the weight ratio of cyclosporin to medium chain or long chain fatty acid mono- or di-glyceride or a combination is from about 3:1 to about 1:3, for example about 3:1 to about 1:2, or about 2.5:1 to about 1:1.8, about 1.5:1 to 1:1.5, about 1.2:1 to 1:1.2, about 1.2:1, about 1:1, or about 1:1.2. Suitably the cyclosporin composition in this example further comprises an oil phase. The oil phase may be any suitable hydrophobic oil, for example an oil having a low HLB value (for example HLB less than 10). Particularly the oil phase may comprise any of the oil phases described herein, for example the oil phase may be or comprise triglycerides, for example a medium chain triglyceride. The weight ratio of oil to surfactant may be for example 12:1 to 1:5, for example from about 5:1 to about 1:5, from about 3:1 to about 1:2, from about 3:1 to about 1:1 or from about 2.5:1 to 1.5:1. The composition may further comprise a solvent. The solvent is suitably an organic solvent in which cyclosporin is soluble. More particularly suitable solvents include those in which both cyclosporin and the oil phase (when present) are soluble. For example the solvent may comprise 2-(ethoxyethoxy)ethanol. The cyclosporin may be partially or fully dissolved in the composition. Accordingly, the cyclosporin may be substantially dissolved in the composition. Suitably the cyclosporin is fully dissolved in the composition.

[00145] The composition is suitably formulated such that release of cyclosporin in the upper GI Tract, for example in the duodenum and jejunum, is minimised so as to minimise the systemic absorption of cyclosporin and both hepatic and enteric P450 metabolism. Accordingly a particular composition is a modified release composition. Suitably the release of cyclosporin from the composition is minimised for the first 4 hours after oral administration such that the composition can pass through the duodenum and jejunum and into the ileum before releasing large amounts of cyclosporin. Preferably the composition releases the majority (for example at least 50 %) of the cyclosporin into the colon. Suitably the composition releases less than 40% (for example less than 35%, or less than 30%) of the cyclosporin from the composition 4 hours when measured in the two stage dissolution test described herein. Suitably the composition releases less than 15% (for example 0 to 10%) of the cyclosporin A after 2 hours; and releases 10% to 40% (for example 10% to 35%, or suitably 15% to 35%) of the cyclosporin A at 4 hours, when measured in the two stage dissolution test.

[00146] The composition may be formulated to provide the desired modified release profile by, for example, use of any of the coatings described herein, in particular coatings which are adapted to release cyclosporin in at least the colon. Suitable coatings include, for example, a modified release coating comprising a pH independent polymer such as ethyl cellulose. The coating may also comprise a first coating comprising a water soluble cellulose ether such as HPMC, as described herein. Other modified release coatings are also contemplated including but not limited to enteric coating systems and other delayed release coatings. Generally the modified release coatings comprise a polymeric coating.

[00147] Also disclosed is when the composition comprises cyclosporin A and a surfactant which is or comprises a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof as described herein, the cyclosporin and surfactant are suitably dispersed within in matrix. The cyclosporin is released from the matrix when the composition is placed in an aqueous environment, for example as would be found in the lower GI tract such as in the colon. Suitable matrix materials which may be used to disperse the cyclosporin and surfactant may be any of the matrix materials described herein, for example those described under "Composition" in the detailed description. In certain examples the matrix material may be selected such that the matrix itself modifies the release of cyclosporin from the composition as described in more detail in the detailed description of the disclosure. In such compositions it may be possible to achieve the desired inhibition of release of cyclosporin in the first 4 hours following oral administration without the need for additional modified release coating(s). In other examples the matrix material may be coated with one or more of the modified release coatings, such as those described herein to provide the required cyclosporin release profile. In a particular, in this example of the disclosure the matrix is a hydrogel polymer, as described herein, more particularly the matrix is or comprises gelatin.

[00148] In a preferred example in this example of the disclosure, the composition comprising cyclosporin may be any of the cyclosporin compositions described herein which comprise a surfactant wherein the surfactant is, or comprises, a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof.

[00149] The cyclosporin compositions described herein, more particularly the modified release compositions described herein, provide pharmacokinetic (PK) properties which minimise systemic exposure to cyclosporin compared to, for example, intravenous administration of cyclosporin and/or oral administration of instant release cyclosporin compositions such as Neoral™. The following paragraphs describing suitable PK properties of the compositions are applicable to any of the cyclosporin compositions described herein.

[00150] The composition may provide a low systemic whole blood exposure to cyclosporin following oral administration of the composition. The composition may provide a mean whole blood cyclosporin A $AUC_{0\text{-}inf}$ of less than about 450 ng.hr/ml, less than about 350 ng.hr/ml, or less than about 300 ng.hr/ml after oral administration of the composition as a single dose containing 75 mg cyclosporin A to a human in a fasted state, or an $AUC_{0\text{-}inf}$ directly proportional thereto for a total dose other than 75mg. For example, the composition may provide a mean whole blood cyclosporin A $AUC_{0\text{-}inf}$ of from about 140 to about 420 ng.hr/ml, for example from about 150 to about 300 ng.hr/ml after oral administration of the composition as a single dose containing 75 mg cyclosporin A to a human in a fasted state, or an $AUC_{0\text{-}inf}$ directly proportional thereto for a total dose other than 75mg.

[00151] A high peak blood concentration of cyclosporin A (C_{max}) may result in undesirable side effects and potentially reduce the therapeutic window available for a composition containing cyclosporin A. Accordingly, the compositions suitably provide a low $C_{max.}$ The composition comprising cyclosporin A, may provide a mean maximum whole blood concentration of cyclosporin A (Cmax) of less than 100 ng/ml. The composition may for example provide a C_{max} of from about 15 to about 60

rpm and a dissolution medium temperature of 37°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 (herein referred to as "the two-stage dissolution test).

[00156] The composition may release less than 20% of the cyclosporin A after 2 hours; releases 10 to 40% of the cyclosporin A at 4 hours; and releases at least 60% of the cyclosporin A at 12 hours, when measured in the two stage dissolution test. The composition may release less than 10% of the cyclosporin A after 2 hours; releases 10 to 30% of the cyclosporin A at 4 hours; and releases at least 50% of the cyclosporin A at 12 hours, when measured in the two stage dissolution test. The composition may release from about 30 to about 75% of the cyclosporin A between 4 hours and 12 hours in the two stage dissolution test, for example the composition releases from about 40 to about 75%, particularly from about 45 to 70% of the cyclosporin A between 4 hours and 12 hours in the two stage dissolution test. The composition may release 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 25% to 70% (for example 40% to 70%) of the cyclosporin A between 4 hours and 12 hours in the two stage dissolution test.

[00157] It is to be understood that any of the individual PK parameters and/or in-vitro or other release profiles described herein may be combined with the compositional features of the cyclosporin compositions described herein, for example relating to any one or a combination of AUC; Cmax; Tmax; cyclosporin A concentration in the luminal contents; cyclosporin A concentration in the GI tract tissue; the ratio of cyclosporin A in the luminal contents : cyclosporin A in GI tract tissues; the ratio of the concentration of cyclosporin A: the concentration of cyclosporin A metabolites in collected faeces; the concentration of cyclosporin A in intracolonic faeces: the concentration of cyclosporin A in colonic tissue; or the concentration of cyclosporin A in colonic tissue. By way of a non-limiting example of such a combination of features composition comprising cyclosporin A, provides a mean concentration of cyclosporin A: the concentration of cyclosporin A metabolites in a faecal sample from the human of greater than 12:1 after oral administration of the composition to the human; and wherein the composition provides an $AUC_{0\text{-}inf}$ of less than about 450 ng.hr/ml, (e.g. from about 140 to about 420 ng.hr/ml) after oral administration of the composition as a single dose containing 75 mg cyclosporin A to a human in a fasted state, or an $AUC_{0\text{-}inf}$ directly proportional thereto for a total dose other than 75mg. Optionally this composition may release 0 to 10% of the cyclosporin A after 2 hours; 10% to 35% of the cyclosporin A at 4 hours; and releases from about 40% to 70% of the cyclosporin A between 4 hours and 12 hours, when measured in the two stage dissolution test.

[00158] In another example the composition releases 0 to 10% of the cyclosporin A after 2 hours; and releases from 50 to 100% of the cyclosporin A after 12 hours, when measured in the two stage dissolution test. In another example the composition releases less than 20% of the cyclosporin A after 2 hours; releases 5 to 40% of the cyclosporin A at 4 hours and releases at least 50% of the cyclosporin A at 12 hours, when measured in the two stage dissolution test.

[00159] The cyclosporin compositions described herein are expected to provide similar or higher levels of cyclosporin A in the colonic tissue compared to IV administration of Sandimmun™, but with a higher intracolonic faecal concentration of cyclosporin A as a result of the local release of the cyclosporin directly into the colon. The relatively high local concentration of cyclosporin in the colon is expected to provide beneficial therapeutic effects.

[00160] The composition comprising cyclosporin A described herein, may provide a ratio of the mean concentration of cyclosporin A present in intracolonic faeces : the mean concentration of cyclosporin A present in colonic tissue in an adult human patient after oral administration of the composition of from about 50:1 to about 500:1, optionally from about 80:1 to about 300:1, or optionally about 100:1 to about 250:1; wherein the concentration of the cyclosporin A is measured in samples of the intracolonic faeces and the colonic tissue taken substantially simultaneously 4 to 6 hours after oral administration of the last dose of a once daily oral dosing regimen of the composition, the dosing regimen comprising once daily oral administration of the composition for seven days. Optionally the once daily oral dosing regimen of the composition provides a single daily dose of 75 mg cyclosporin A. However, other doses may be administered for example any of the cyclosporin doses described herein including but not limted to 37.5 mg or 150 mg once per day. Optionally the dosage regimen may be a twice daily dosage regimen for seven days, for example 37.5 mg twice per day, 75 mg twice per day or 150 mg twice per day.

[00161] Reference herein to a sample being taken "substantially simultaneously" means that the samples are obtained close to the same time point, for example the colonic tissue and/or intracolonic faeces and/or blood samples are taken within about 2 hours, 1 hour or 30 minutes of each other, suitably the samples are all taken at the same time point.

[00162] In contrast to the compositions according to the disclosure, IV administration cyclosporin as Sandimmun™ results in a lower ratio of the mean concentration of cyclosporin A present in intracolonic faeces : the mean concentration of cyclosporin A present in colonic tissue. As illustrated in the Examples, when patients were treated with Sandimmun® IV (2mg/kg) administered as an infusion over 24 hours (2mg/kg/day) a ratio of about 3:1 was observed.

[00163] Accordingly, the orally administered cyclosporin compositions described herein are expected to provide a relatively high colonic tissue concentrations compared to IV administration of an equivalent dose of cyclosporin (e.g. as Sandimmun™ IV).

[00164] The composition comprising cyclosporin A may provide a concentration of cyclosporin A in colonic tissue of at least 250 ng/g following oral administration of the composition to a human, for example at least 300, 350, 400 or 450 ng/g. Accordingly, the composition may provide a cyclosporin A concentration of from about 250 to 6000 ng/g, for example from 400 ng/g to 6000 ng/g, from 500 to 5000 ng/g, from 600 to 4000 ng/g, or from 600 to 2000 ng/g. Particularly the composition provides a cyclosporin A concentration in colonic tissue of from about 1000 to about 1500 ng/g, for example about 1200 ng/g. Suitably the compositon is orally administered to provide a daily dose of cyclosporin A within the ranges described herein, suitably a total daily dose in the range of 15 to 300 mg

cyclosporin. Optionally the composition provides a dose may be 37.5 mg, 75 mg or 150 mg cyclosporin A once or twice per day.

[00165] The colonic tissue samples described above may be obtained using conventional methods, for example by taking a tissue sample during endoscopy as described in the examples herein.

[00166] As described above, compositions comprising cyclosporin A and a surfactant, wherein the surfactant comprises, or is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof may inhibit P450 metabolism of cyclosporin A. Such compositions may be useful for the preparation of modified release of cyclosporin in the lower GI tract as described above. Also contemplated are such compositions for administration of cyclosporin to any part of the GI tract, for example duodenum or jejunum as, for example, an instant release composition. The compositions may reduce the rate and or extent of cyclosporin metabolism and thereby maximise the amount of cyclosporin in the GI tract.

[00167] According to a further feature of the disclosure there is provided a composition comprising cyclosporin A and a surfactant, wherein the surfactant comprises, or is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof. Suitably the composition does not comprise or is not a polyethyleneglycol ether or ester. Suitably the surfactant is present in an amount of at least 6% by weight of the composition, for example at least 10%, at least 15% or at least 20% by weight of the composition. Optionally the surfactant is present in an amount of from 10 to about 50% by weight.

[00168] The composition according to this example of the disclosure may further comprise an oil phase, for example any of the oil phases described herein.

[00169] The cyclosporin may be partially or completely dissolved in the composition. Suitably the cyclosporin is completely dissolved in the composition.

[00170] A particular composition comprises:

(i) 10 to 60 parts cyclosporin A;

(ii) 5 to 40 parts of a medium chain fatty acid triglyceride, for example a caprylic/capric triglyceride;

(iii) 10 to 50 parts of the surfactant; and

(iv) 0 to 60 parts solvent;

wherein all parts are parts by weight and the sum of the parts (i) + (ii) + (iii) + (iv) = 100.

[00171] Another composition comprises:

(i) 10 to 40 parts cyclosporin A;

(ii) 5 to 25 parts of a medium chain fatty acid triglyceride, a caprylic/capric triglyceride;

(iii) 15 to 30 parts of the surfactant; and

(iv) 10 to 60 parts solvent (optionally 20 to 40 parts or 25 – 30 parts solvent), for example 2-(2-ethoxyethoxy)ethanol);

wherein all parts are parts by weight and the sum of the parts (i) + (ii) + (iii) + (iv) = 100.

[00172] Optionally in this example the surfactant is selected from glyceryl caprylate, glyceryl caprate, glyceryl monooleate, glyceryl dioleate and glycerol monolinoleate, or a combination thereof.

[00173] The cyclosporin compositions according to this example may be administered orally, for example to provide an instant release composition. Also contemplated is the administration of the composition to the GI tract rectally, for example in the form of an enema or suppository. Other routes of administration of the composition are also contemplated, for example the composition may be administered directly to the GIT, by for example intra-duodenal administration, intra-jejunal or intra-ileal administration. Such routes of administration enable the compositon to bypass the stomach (and optionally other parts of the GI tract) for delivery to specific points in the lower GI tract. These routes of administration may be achieved using for example suitable tubing with an exit at the desired location within the GI tract. Suitably the tubing is inserted orally or nasally into the GI Tract. Alternatively, administration may be achieved by gastric tubing, or continuous or discontinuous percutaneous endoscopic gastrostomy (PEG) tubing. PEG is an endoscopic medical procedure in which a tube (PEG tube) is passed into a patient's stomach through the abdominal wall. This method of administration may be particularly suitable for patients that cannot take the drug orally due to for example dysphagia or sedation.

[00174] Also disclosed is a composition described herein for use as a medicament. The composition may comprise at least one further active ingredient, for example at least one further immunosuppressant. In particular there is provided a composition for use in the treatment, e.g. prevention, of a condition of the GIT. The composition may be for use in the treatment of an inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, ulcerative colitis, celiac disease, graft-versus-host disease, gastrointestinal graft-versus-host disease, gastroenteritis, duodenitis, jejunitis, ileitis, peptic ulcer, Curling's ulcer, appendicitis, colitis, pseudomembraneous colitis, diverticulosis, diverticulitis, pouchitis, collagenous colitis, macorscopic colitis, diarrheal colitis, endometriosis, colorectal carcinoma and adenocarcinoma. The composition may also be for use in the treatment of proctitis. The composition may be for use in the prevention or treatment of primary sclerosing cholangitis, familial adenomatous polyposis, or perinanal Crohn's, including perianal fistulae.

[00175] In examples where the pharmaceutical composition does not comprise a second coating, the composition may be for use in the treatment of conditions that affect the small intestine. Such compositions may be able to treat conditions selected from celiac disease, GVHD or Crohn's disease.

[00176] The disclosure additionally provides a method for administering cyclosporin to a subject, comprising orally administering to the subject a composition described herein. The method may be performed in the treatment, e.g. prevention, of disease. The subject may be a mammal, in particular a human. Also provided is a method for treating a condition of the GI tract in a subject, preferably a human, in need thereof comprising orally administering to the mammal a therapeutically effective amount of a composition described herein. Conditions of the GI tract which may be treated or prevented include the conditions disclosed herein.

[00177] Also disclosed is the use of a composition described herein for use in the manufacture of a medicament for the treatment, e.g. prevention, of a condition of the GIT. Conditions of the GI tract include those disclosed herein.

[00178] The disclosure also contemplates a method of treating a condition selected from inflammatory bowel disease, irritable bowel disease, Crohn's disease, ulcerative colitis, celiac disease, graft vs host disease, gastrointestinal graft-versus-host disease, gastroenteritis, duodenitis, jejunitis, ileitis, peptic ulcer, Curling's ulcer, appendicitis, colitis, pseudomembraneous colitis, diverticulosis, diverticulitis, collagenous colitis, endometriosis, colorectal carcinoma and adenocarcinoma, wherein the method comprises administering a pharmaceutical composition of the disclosure.

[00179] Also disclosed is a method of treating conditions that affect the small intestine, wherein the method comprises administering a composition of the disclosure which does not comprise a second coating. The conditions of the small intestine may be selected from celiac disease, GVHD or Crohn's disease.

[00180] Also disclosed is a process for making a liquid composition, the process comprising mixing an oil phase with an aqueous phase comprising a hydrogel forming polymer, wherein the oil phase has cyclosporin in solution and comprises a surfactant which is medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof, wherein the surfactant does not comprise or is not a polyethyleneglycol ether or ester.

[00181] Optionally, the oil phase and the aqueous phase are mixed in an oil phase to aqueous phase ratio of from 1:2 to 1:12, optionally 1:4 to 1:10, 1:4 to 1:8, for example 1:5 or 1:7.

[00182] The process may further comprise the step of causing the emulsion to solidify.

[00183] The process may further comprise the step of:

coating a core with a coating comprising HPMC wherein the weight gain due to the coating is from 0.5% to 20% of the weight of the pharmaceutical composition. The core may comprise a pharmaceutically active ingredient and may be a core as described in this specification.

[00184] An additional advantage of the present application may be that a composition dissolved in a dissolution medium yields a uniform droplet size with low polydispersivity compared to formulations with a different first surfactant.

[00185] Accordingly, there is provided a composition comprising cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix, wherein the surfactant is or comprises a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethyleneglycol ether or ester,

wherein the composition releases droplets with a uniform size. Optionally the droplets may have low polydispersity. Optionally the uniform size may be a droplet size of from about 1 nm to about 350 nm.

[00186] The droplet size may be selected from: from about 20 nm to about 350 nm; from about 20 nm to about 300 nm; from about 20 nm to about 250 nm from about 100 nm to about 350 nm; from about 100 nm to about 300 nm; from about 100 nm to about 250 nm; from about 100 nm to about 200 nm; from about 150 nm to about 250 nm; from about 150 nm to about 200 nm; from about 150 nm to about 350 nm; and from about 150 nm to about 300 nm. Preferably, the droplet size may be selected

from: from about 20 nm to about 250 nm; from about 100 nm to about 250 nm; and from about 100 nm to about 200 nm.

[00187] The size of the droplets may be measured using dynamic light scattering. The dynamic light scattering experiments were carried out by analysis of a liquid medium arrived at as follows. Minibeads of the disclosure (0.5 g) comprising Capmul GMO-50 as the first surfactant were added to a beaker containing 50 g of deionised water. The beaker contents were mixed at 250 rpm and at 37 °C throughout the study. Samples of the beaker contents were taken at 0, 1, 2, 3, 4, 5, 6 and 24 hours. Samples of the beaker contents were filtered 0.65µm pore size filters (Merck Millipore Ultrafree-CL Centrifugal Filter). The particle size and zeta potential was measured using a Malvern Nano-Zetasiser.

[00188] For certain active ingredients it may be desirable to limit or delay release of the active from the composition until the composition has passed through the stomach and upper GI tract. The compositions of the disclosure comprising a second coat may be particularly suitable for such applications. The second coat acts to delay release from the composition, whilst the presence of the coating of the disclosure (e.g. HPMC) increases the amount of active released when the composition releases the active in the lower GI tract. The period of delay to the release of the active as a result of the presence of the second coating can be tailored by appropriate selection of the nature or amount of second coating used. For a given second coating material a higher weight gain of coating will generally increase the time period between administration of the composition and release of the active. The compositions of the disclosure can therefore be used to provide high levels of release of active agent at very specific parts of the GI tract to provide, for example, topical treatment to diseased tissue within the GI tract. Such delayed release compositions may be particularly beneficial when the active has undesirable side effects which may arise from systemic absorption higher in the GI tract.

[00189] Included in this description by reference are the subject matters of the appended claims. The description is therefore to be read together with the claims and features mentioned in the claims are applicable to the subject matters of the description. For example, a feature described in a process claim is applicable also to products mentioned in the description, where the feature is manifested in the product. For example, a feature mentioned in a product claim is applicable also to relevant process subject matters contained in this description. Similarly, a feature mentioned in the description in the context of a process is applicable also to products mentioned in the description, where the feature is manifested in the product. Also, a feature mentioned in the description in the context of a product is applicable also to relevant process subject matters contained in this description.

BRIEF DESCRIPTION OF THE DRAWINGS

[00190] Embodiments of the invention are further described hereinafter with reference to the accompanying drawings, in which:

Figure 1 is an image showing crystal formation over time of a comparative composition.

Figure 2 is an image showing crystal formation over time of a composition of the invention comprising Capmul GMO-50 (glyceryl monooleate/dioleate) as the surfactant (the first surfactant).

Figure 3 is an image showing crystal formation over time of a composition of the invention comprising Capmul MCM (glyceryl caprylate/caprate) as the surfactant (the first surfactant).

CLAIMS

1. A solid oral composition comprising cyclosporin, a hydrogel forming polymer matrix, a surfactant and an oil phase being dispersed in the hydrogel forming polymer matrix, wherein the surfactant comprises or is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not 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 or is 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 is or 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 is or 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 is or comprises a liquid lipid and optionally wherein the liquid lipid is or comprises a glyceride composition,
   further optionally wherein the liquid lipid is or comprises a medium chain fatty acid triglyceride

or a combination thereof, or the liquid lipid is or 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 is or 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 a hydrogel forming polymer matrix is or 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 or is 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 or is 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 or is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not 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 is or comprises a composition according to any of claims 1 to 17.

20. The composition of any preceding claim, 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°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 or being a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and not comprising or not being a polyethylene glycol ether or ester.

23. The process of claim 21, 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.

25. A liquid composition comprising an aqueous phase, a surfactant and an oil phase in which cyclosporin is dissolved, wherein the oil phase comprises a liquid lipid and the surfactant comprises or is a medium chain or long chain fatty acid mono- or di-glyceride or a combination thereof and does not comprise or is not a polyethylene glycol ether or ester, the aqueous phase comprises a hydrogel-forming polymer and the oil phase is dispersed in the aqueous phase; wherein the hydrogel-forming polymer is in an amount of at least 25% by weight based upon the dry weight of the composition.