infections caused by a virus or bacteria can be treated with antibiotic or antiviral drops, ointment or oral medication. While such treatments may be effective in helping to fight the infection, they may not be effective in combating associated inflammation, discomfort or dryness.

[0019] Jabs et al, “Guidelines for the Use of Immunosuppressive Drugs in Patients with Ocular Inflammatory Disorders: Recommendations of an Expert Panel”, Am J Ophthalmol, 130(4): 492-513, 2000, provide recommendations for the use of immunosuppressive drugs in the treatment of patients with ocular inflammatory disorders.

[0020] WO 2017/157997 A1 discloses non-aqueous topical compositions comprising a halogenated salicylanilide, such as niclosamide, and the use of such compositions in the topical treatment or prevention of an infection or disease caused by Gram-positive bacteria.

[0021] US 4742083 suggests the use of certain substituted salicylamides as systemic analgesic agents and also for topical application as anti-inflammatory compositions.

~~BRIEF~~ SUMMARY ~~OF THE DISCLOSURE~~

[0021a] In a first aspect, the present disclosure refers to a formulation comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and a cyclodextrin.

[0021b] In another aspect, the present disclosure refers to a formulation comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and a cyclodextrin, for use as a medicament, wherein the formulation is as disclosed herein.

[0021c] In a further aspect, the present disclosure refers to a use of a formulation comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and a cyclodextrin, in the manufacture of a medicament for the treatment or prevention of an infectious disease or an inflammatory disease in a subject in need thereof, wherein the formulation is as disclosed herein.

[0021d] In yet another aspect, the present disclosure refers to a use of a formulation comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and a cyclodextrin, in the manufacture of a medicament for the treatment or prevention of an infectious ocular disease or an inflammatory ocular disease in a subject, wherein the formulation is as disclosed herein.

[0021e] In another aspect, the present disclosure refers to an aerosol of a solution comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and cyclodextrin.

[0021f] In a further aspect, the present disclosure refers to a use of the aerosol as disclosed herein, in the manufacture of a medicament for the treatment or prevention of an infectious disease or an inflammatory disease in a subject, optionally a pulmonary infectious or inflammatory disease, wherein the aerosol is to be administered to the subject by inhalation.

[0021g] In yet another aspect, the present disclosure refers to a system comprising:

- a formulation as disclosed herein; and

- an inhaler device and/or an intranasal delivery device.

[0021h] In another aspect, the present disclosure refers to a method of preparing a formulation, the method comprising:

- adding cyclodextrin and/or a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, to a solvent to form a suspension;

- heating the suspension for a period of time sufficient for the cyclodextrin and/or a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, to dissolve in the solvent, thereby forming a solution;

- optionally, adding one or more polymers to the suspension or the solution, optionally wherein the polymer comprises PVP;

- optionally, raising the pH of the suspension or solution, optionally wherein the pH is raised to a pH of 8-13; and

- cooling the solution.

[0021i] In a further aspect, the present disclosure refers to a formulation as disclosed herein, or an aerosol as disclosed herein, for use in therapy.

[0022] According to a first ~~aspect~~ example of the present ~~invention~~ disclosure there is provided a formulation comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and a cyclodextrin.

[0023] The halogenated salicylanilide may be selected from the group consisting of niclosamide, closantel, oxyclozanide and rafoxanide, or a pharmaceutically acceptable salt thereof. Preferably, the halogenated salicylanilide is niclosamide, or a pharmaceutically acceptable salt thereof.

[0024] In some examples~~embodiments~~, the niclosamide is present in the free-acid form. Alternatively, the formulation may comprise a pharmaceutically acceptable salt of niclosamide, preferably niclosamide ethanolamine.

[0025] The formulation may be in a form suitable for pulmonary administration. For example, it may be that the formulation is in the form of a solid (e.g. a powder).

[0026] In some examples ~~embodiments~~ the formulation is in the form of a suspension, a dispersion or a solution comprising the halogenated salicylanilide (e.g. niclosamide) or a pharmaceutically acceptable salt thereof, and a cyclodextrin in a pharmaceutically acceptable solvent. In other words, the formulation may be a liquid formulation. Solutions and suspensions comprising a halogenated salicylanilide (e.g. niclosamide) or a pharmaceutically acceptable salt thereof, and a cyclodextrin, may be any of the solutions or suspensions as described herein.

[0027] The pharmaceutically acceptable solvent may comprise water, i.e. the solution or suspension may be an aqueous solution or an aqueous suspension. In some examples~~embodiments~~ the solvent is water. In some examples~~embodiments~~, the solvent comprises a co-solvent. Certain co-solvents may be useful to aid solubilisation of the halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and/or the cyclodextrin, and/or to help stabilise the solution. In certain examples ~~embodiments~~ the co-solvent is selected from ethanol, propylene glycol, glycerol, polyethylene glycol (e.g. a polyethylene glycol (PEG) with an average molecular weight of less than 600, such as PEG 200, PEG 300 or PEG 400. In some examples ~~embodiments~~ the co-solvent is selected from propylene glycol and glycerol. In some examples ~~embodiments~~ the co-solvent is not a PEG. In some examples ~~embodiments~~ the co-solvent is not ethanol. In certain examples ~~embodiments~~ the co-solvents is DMSO. A co-solvent may be present in the formulation in an amount of from about 0 % to about 20 %, from about 0.1 % to about 15 %, from about 0.2 % to about 12 % by weight, from about 0.3 % to about 10 %, from about 0.4 % to about 8 %, from about 0.5 % to about 6 %, from about 0.6 % to about 5 %, from about 0.7 % to about 4 %, from about 0.8 % to about 2 %, from about 0.9 % to about 1 % by weight, based on the weight of the solution or suspension.

[0028] In certain examples~~embodiments~~ the halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, is present in the formulation an amount of about 0.01 % to about 10 % by weight of the formulation. For example, the halogenated salicylanilide (e.g. niclosamide) or a pharmaceutically acceptable salt thereof is present in an amount of 0.05 % to 10 %, 0.1 % to 9 %, 0.05 % to 8 %, 0.5 % to 8 %, 1 % to 8 %, 1.5 % to 8 %, 2 % to 8 %, 2.5 % to 8 %, 3 % to 8 %, 3.5 % to 8 %, 4 % to 8 %, 4.5 % to 8 %, 5 % to 8 %, 5.5 % to 8 %, 6 % to 8 %, 3 % to 7 %, 3.5 % to 7.5 %, 3.5 % to 7 %, 3.5 % to 6.5 %, 3.5 % to 6 %, 3.5 % to 5.5 %, 4 % to 7 %, 4 % to 7 %, 4 % to 6.5 %, 4 % to 6 %, 4 % to 5.5 %, 4.5 % to 7 %, 4.5 % to 6.5 %, 4.5 % to 6.5 % or 4.5 % to 5.5 % by weight of the formulation.

[0029] In some examples~~embodiments~~ the halogenated salicylanilide (e.g. niclosamide) or a pharmaceutically acceptable salt thereof is present in the formulation in an amount of from about 0.05 to about 5 %, from about 0.5 to about 4%, from about 0.1 to about 3%, from about 0.2 to about 2 %, from about 0.5 to about 1.8%, from about 0.5 to about 1.5%, from about 0.8 to about 1.5%, from about 0.8 to about 1.2%, from about 0.9 to 1.1%, from about 1 to about 3% or from about 1.5 to about 2% by weight of a liquid formulation. Thus it may be that the halogenated salicylanilide (e.g. niclosamide) or a pharmaceutically acceptable salt is present in the liquid formulation in an amount of about 0.1%, about 0.2%, about 0.3 %, about 0.4 %, about 0.5 %, about 0.6 %, about 0.7 %, about 0.8 %, about 0.9 %, about 1%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6% about 1.7%, about 1.8% about 1.9%, about 2 %, about 2.1%, about 2.2%, about 2.3%, about 2.4%, about

2.5 %, about 3 %, about 4% or about 5 % by weight of the liquid formulation. In a preferred example ~~embodiment~~ the liquid formulation comprises about 1 % by weight of the halogenated salicylanilide (e.g. niclosamide) or a pharmaceutically acceptable salt thereof. The amounts of the halogenated salicylanilide present in the liquid formulation is applicable to any of the formulations described herein, for example a solution comprising niclosamide or a pharmaceutically acceptable salt thereof; a suspension comprising niclosamide or a pharmaceutically acceptable salt thereof; an aerosol of a solution comprising niclosamide or a pharmaceutically acceptable salt thereof; or an aerosol of a suspension comprising niclosamide or a pharmaceutically acceptable salt thereof;

[0030] In certain examples ~~embodiments~~ the liquid formulations of the present disclosure ~~invention~~ provide high concentrations of solubilised halogenated salicylanilide. In certain examples ~~embodiments~~ the halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, is present in the liquid formulation at a concentration of from about 0.1 to about 100 mg/ml, from about 0.2 to about 90 mg/ml, from about 0.3 to about 80 mg/ml, from about 0.5 to about 75 mg/ml, from about 0.6 to about 70 mg/ml, from about 0.7 to about 65 mg/ml, from about 0.8 to about 60 mg/ml, from about 0.9 to about 60 mg/ml, or from about 1 to about 50 mg/ml. In some examples~~embodiments~~, the halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, is present in the liquid formulation at a concentration of from about 2 to about 45 mg/ml, from about 3 to about 40 mg/ml, from about 4 to about 40 mg/ml, from about 4 to about 35 mg/ml, from about 5 to about 30 mg/ml, from about 5 to about 25 mg/ml, from about 5 to about 15 mg/ml, from about 7 to about 20 mg/ml, from about 7 to about 15 mg/ml, from about 8 to about 15 mg/ml, from about 9 to about 12 mg/ml, or from about 10 to about 11 mg/ml.

[0031] In some examples ~~embodiments~~ the halogenated salicylanilide (e.g. niclosamide) or a pharmaceutically acceptable salt thereof is present in the formulation in an amount of about 0.05 to 5 % by weight of a solid formulation. Thus it may be that the halogenated salicylanilide (e.g. niclosamide) or a pharmaceutically acceptable salt is present in the solid formulation in an amount of about 0.05 % to 10 %, 0.05 % to 8 %, 0.5 % to 8 %, 1 % to 8 %, 1.5 % to 8 %, 2 % to 8 %, 2.5 % to 8 %, 3 % to 8 %, 3.5 % to 8 %, 4 % to 8 %, 4.5 % to 8 %, 5 % to 8 %, 5.5 % to 8 %, 6 % to 8 %, 3 % to 7 %, 3.5 % to 7.5 %, 3.5 % to 7 %, 3.5 % to 6.5 %, 3.5 % to 6 %, 3.5 % to 5.5 %, 4 % to 7 %, 4 % to 7 %, 4 % to 6.5 %, 4 % to 6 %, 4 % to 5.5 %, 4.5 % to 7 %, 4.5 % to 6.5 %, 4.5 % to 6.5 %, 4.5 % to 6 % or 5 to 5.5 % by weight of the solid formulation. The amounts of the halogenated salicylanilide present in the solid formulation is applicable to any of the solid formulations described herein, for example a powder comprising niclosamide or a pharmaceutically acceptable salt thereof.

[0032] In some examples~~embodiments~~, the formulation is suitable for aerosol administration.

[0033] The cyclodextrin may be α-, β- or γ-cyclodextrin, or a derivative thereof. In some examples~~embodiments~~, the cyclodextrin is β-cyclodextrin, or a derivative thereof. In some examples~~embodiments~~, the cyclodextrin is 2-hydroxypropyl- β -cyclodextrin (HP-β-CD). In some examples ~~embodiments~~ the cyclodextrin is sulfobutylether-β-CD. In some examples ~~embodiments~~ the cyclodextrin is not sulfobutylether-β-CD.

[0034] In some examples ~~embodiments~~ the cyclodextrin is present in an amount of about 1 % to about 90 % by weight of the formulation. For example, the cyclodextrin may be present in an amount of from about 5 % to about 85 %, from about 10 % to about 80 % or from about 20 % to about 70 % by weight, based on the weight of the formulation.

[0035] In certain examples ~~embodiments~~ the cyclodextrin is present in an amount of about 1 % to about 60 % by weight of a liquid formulation. In certain examples~~embodiments~~ the cyclodextrin is present in an amount of more than about 5%, more than about 6%, more than about 7%, more than about 8%, more than about 9%, more than about 10%, more than about 11%, more than about 12%, more than about 13%, more than about 14% or more than about 15% by weight of a liquid formulation. In certain examples ~~embodiments~~ the cyclodextrin is present in an amount of about 1 % to about 25 % by weight of a liquid formulation. For example, the cyclodextrin is present in an amount of 2 % to 24 %, 3 % to 23 %, 4 % to 22 %, 5 % to 21 %, 6 % to 20 %, 7 % to 19.5 %, 8 % to 19 %, 9 % to 18.5 %, 10 % to 18 %, 10.5 % to 17.5 %, 11 % to 17 %, 11.5 % to 16.5 %, 12 % to 16 %, 12.5 % to 15.5 %, 13 % to 15 % or 13.5 % to 14.5 %, by weight of the liquid formulation. In certain examples ~~embodiments~~ the cyclodextrin is present in an amount of about 10%, about 10.5%, about 11%, about 11.5%, about 12%, about 12.5%, about 13%, about 13.5%, about 14%, about 14.1%, about 14.2%, about 14.3%, about 14.4%, about 14.5%, about 14.6%, about 14.7%, about 14.8%, about 14.9%, about 15%, about 15.1%, about 15.2%, about 15.3%, about 15.4%, about 15.5%, about 15.6%, about 15.7%, about 15.8%, about 15.9%, about 16%, about 16.5% about 17%, about 17.5% or about 18%, by weight of the liquid formulation.

[0036] In a preferred example ~~embodiment~~ the cyclodextrin is present in the liquid formulation in an amount of about 14.5 % to 15.5 % by weight of the liquid formulation.

[0037] In certain examples ~~embodiments~~ the cyclodextrin is present in an amount of about 50 % to about 95 % by weight of a solid formulation. For example, the cyclodextrin may be present in an amount of from about 55 % to about 90 %, from about 60 % to about 85 %, from about 65 % to about 80 % or from about 70 % to about 75 % by weight, based on the weight of the solid formulation.

[0038] In some examples ~~embodiments~~ the liquid formulation comprises from about 0.1 % to about 1.5 % by weight of niclosamide ethanolamine and from about 10 % to about 20 % by weight of cyclodextrin (e.g. HP-β-CD).

[0039] In some examples ~~embodiments~~ the liquid formulation comprises from about 0.1 % to about 1.5 % by weight of niclosamide ethanolamine and from about 12 % to about 20 % by weight of cyclodextrin (e.g. HP-β-CD). In a preferred example ~~embodiment~~ the liquid formulation comprises about 1 % by weight of niclosamide ethanolamine and about 15 % by weight of cyclodextrin (preferably HP-β-CD).

[0040] At least a portion of the halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof may form a complex with the cyclodextrin. In some examples~~embodiments~~, from about 20 to about 100 %, from about 30 % to about 90%, from about 40 % to about 80% or from about 50 % to about 70% of the halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt thereof, is complexed with the cyclodextrin.

[0041] In some examples ~~embodiments~~ the ratio of halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, to cyclodextrin is from 1:250 to 5:1, from 1:200 to 4:1, from 1:150 to 3:1, from 1:100 to 2:1, from 1:50 to 1:1, from 1:30 to 1:2, from 1:20 to 1:3, from 1:20 to 1:8, from 1:20 to 1:12, from 1:18 to 1:12, from 1:15 to 1:4 or from 1:10 to 1:5.

[0042] In some examples~~embodiments~~, the formulation comprises at least one stabilizer. Suitable stabilizers include polymers, emulsifiers, surfactants and combinations thereof. In some examples ~~embodiments~~ the stabilizer comprises a polymer. Suitably the polymer is a water soluble polymer, preferably a polymer that is soluble in water at the pH of the liquid formulations disclosed herein. Advantageously, the addition of a polymer may improve the stability of a solution comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin. Without being bound by theory, it is thought that the presence of the stabilizer (e.g. polymer) may aid complex formation between the halogenated salicylanilide and cyclodextrin, and thus may also assist in preparing the formulation. Additionally or alternatively, the stabilizer (e.g. polymer) may help to inhibit crystallisation and subsequent precipitation of the solubilised halogenated salicylanilide. Accordingly formulations comprising a stabilizer such as a polymer may provide high concentration of solubilised halogenated salicylanilide in the formulations of the present disclosure~~invention~~. The polymer may be selected from the group consisting of polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA), hydroxypropylcellulose (HPC), poloxamers, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose acetate succinate (HPMC-AS), polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA) and any combination

thereof. Preferably, the polymer comprises PVP. As is known in the art, PVP is available in several viscosity grades, ranging from low to high molecular weight. Available PVP grades include K-12, K-15, K-17, K-30, K-60, K-80, K-85, K-90 and K-120. In some examples~~embodiments~~, the formulation comprises PVP K-12, K-15, K-17 or K-30. The K-value refers to the Fikentscher K value and may be determined by measuring the viscosity of a 1% wt./vol pf the PVP in water using Ostwald-Fenske or Cannon-Fenske capillary viscometer and calculating the K-value, for example using the method described in ISO 1628-1:2009. In some examples~~embodiments~~, the polymer is PVP/VA. As is known in the art, PVP/VA copolymers are available in different ratios of vinylpyrrolidone to vinyl acetate. The weight ratio of PVP : VA may be 70:30, 60:40, 50:50, 40:60 or 30:70. In some examples~~embodiments~~, the ratio is 60:40 (e.g. available as Kollidon® VA 64).

[0043] The polymer may be present in the formulation in an amount of from about 0.01 % to about 20 %, from about 0.05 % to about 18 %, from about 0.1 % to about 15 %, from about 0.5 % to about 13 %, from about 0.8% to about 12%, from about 1% to about 10%, from about 2 % to about 8% or from about 3 % to about 6 % by weight based on the weight of the formulation.

[0044] For example, the polymer may be present in a liquid formulation in an amount of from about 0.01 % to about 10 %, from about 0.05 % to about 8 %, from about 0.1 % to about 6 %, from about 0.1% to about 5%, from about 0.1% to about 4%, from about 0.1% to about 3%, from about 0.5% to about 5%, from about 0.5 % to about 4 %, from about 0.5% to about 3%, from about 0.8% to about 3%, from about 1% to about 4%, from about 1% to about 3%, from about 1% to about 2.5%, or from about 1% to about 2% by weight based on the weight of the liquid formulation. Thus it may be that the polymer is present in a liquid formulation in an amount of about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1% about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, about 2% about 2.1%, about 2.2%, about 2.3%, about 2.4%, about 2.5%, about 2.6%, about 2.7%, about 2.8%, about 2.9%, about 3%, about 3.5%, about 4%, about 4.5% or about 5% by weight based on the weight of the liquid formulation.

[0045] The polymer may be present in a solid formulation in an amount of from about 1 % to about 20 %, from about 2 % to about 18 %, from about 3 % to about 16 %, from about 5 % to about 14 %, from about 5% to about 12%, from about 6% to about 11%, from about 7 % to about 10 % or from about 8 to about 9 % by weight, based on the weight of the solid formulation.

[0046] In some examples ~~embodiments~~ the formulation further comprises a preservative. Suitable preservatives include benzalkonium chloride.

[0047] The preservative may be present in an amount of from about 0 to about 0.2 %, from about 0.002 % to about 0.15 %, from about 0.004 to about 0.1%, from about 0.006 % to about 0.05 %, or from about 0.008 % to about 0.02 % by weight (e.g. about 0.01 wt.%), based on the weight of the formulation.

[0048] In some examples ~~embodiments~~ the formulation further comprises a buffer and/or a stabilising agent. Suitable buffers and stabilising agents include disodium edetate, disodium phosphate, polysorbate 80, sodium dihydrogen phosphate, sodium citrate, sodium phosphate, sodium acetate, acetic acid, histidine lactic acid, aspartic acid, tartaric acid, glutamic acid, succinic acid, malic acid, tromethamine, lactic acid, histidine, fumaric acid and citric acid. Preferably the stabilising agent comprises disodium edetate.

[0049] The stabilising agent may be present in an amount of from about 0 to about 2 % by weight, for example from about 0.02 % to about 1 %, from about 0.04 % to about 0.6 %, from about 0.06 % to about 0.4 %, or from about 0.08 % to about 0.2 % by weight (e.g. 0.1 wt.%), based on the weight of the formulation.

[0050] In some examples ~~embodiments~~ the formulation further comprises an electrolyte. Suitable electrolytes include sodium chloride, potassium chloride, sodium dihydrogen phosphate or potassium dihydrogen phosphate. Preferably the electrolyte is sodium chloride.

[0051] The electrolyte may be present in an amount of from about 0 % to about 10 %, from about 0.1 % to about 8 %, from about 0.2 % to about 5 %, from about 0.3 to about 2 %, from about 0.4 to about 1 %, or from about 0.5 to about 0.8 % by weight, based on the weight of the formulation.

[0052] In some examples ~~embodiments~~ the formulation has a viscosity of from 1 to 150 cP, from 1.5 to 100, from 2 to 50 cP or from 5 to 25 cP. In some examples~~embodiments~~, the formulation has a viscosity of no greater than 20, no greater than 15, or no greater than 10 cP. For example, the viscosity may be from 1 to 10, from 1.5 to 9.5, from 2 to 8, from 2.5 to 7.5, from 3 to 7, from 3.5 to 6.5, from 4 to 6 or from 5.5 to 6.5 cP

[0053] In some examples ~~embodiments~~ the formulation has a pH of from 4 to 9, for example from 5 to 8.5, from 7 to 8.5, or from 6 to 8, e.g. from 4 to 8, from 7 to 8.2, from 7.5 to 8.2, from 7.5 to 7.8, or preferably from 7.6 to 8.

[0054] In some examples ~~embodiments~~ the formulation comprises a pH modifier. Suitable pH modifiers include acids (e.g. hydrochloric acid, acetic acid, lactic acid, citric acid, tartaric acid, malic acid, formic acid, uric acid) and bases (e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium or potassium carbonate, sodium or potassium bicarbonate). In some examples~~embodiments~~, the formulation comprises at multiple (e.g. 2, 3 or 4)

pH modifiers. For example, the formulation may comprise two different acids, or two different bases, or an acid and a base. In some examples~~embodiments~~, the formulation comprises sodium hydroxide and hydrochloric acid.

[0055] In some examples ~~embodiments~~ the formulation has an osmolarity of from 5 to 500 mOsmol/L, from 100 to 400 mOsmol/L, or from 150 to 350 mOsmol/L, for example from 180 to 320 mOsmol/L, from 250 to 350 mOsmol/L, from 280 to 330 mOsmol/L, from 290 to 320 mOsmol/L, or from 200 to 250 mOsmol/L.

[0056] In some examples ~~embodiments~~ the halogenated salicylanilide is niclosamide, or a pharmaceutically acceptable salt thereof. In some examples ~~embodiments~~ the halogenated salicylanilide is niclosamide. In some examples ~~embodiments~~ the halogenated salicylanilide is a pharmaceutically acceptable salt of niclosamide. In some examples ~~embodiments~~ the halogenated salicylanilide is niclosamide ethanolamine.

[0057] According to a second ~~aspect~~ example of the present ~~invention~~disclosure, there is provided a formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin, for use as a medicament. The formulation may be any of the formulations described herein.

[0058] According to a third ~~aspect~~ example of the present ~~invention~~disclosure, there is provided a formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin, for use in the treatment or prevention of an infectious disease or an inflammatory disease in a subject in need thereof. The formulation may be any of the formulations described herein.

[0059] According to a fourth ~~aspect~~ example of the present ~~invention~~disclosure, there is provided a formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin, for use in the treatment or prevention of an ocular condition or disease in a subject. The formulation may be any of the formulations described herein.

[0060] Also provided is a method of treating or preventing an infectious disease, an inflammatory disease or an ocular disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of a formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin. The formulation may be any of the formulations described herein.

[0061] The formulation may be used for the topical treatment or prevention of the infectious disease, inflammatory disease or ocular disease or condition.

[0062] The formulation for use as a medicament, or for use in the treatment or prevention of an infectious, inflammatory or ocular disease may be any formulation as defined herein.

[0063] In some examples~~embodiments~~, the infectious disease is a viral, bacterial, or fungal infection.

[0064] In some examples~~embodiments~~, the infectious disease is a viral infection. The viral infection may be a pulmonary viral infection.

[0065] In certain examples ~~embodiments~~ the viral infection may be caused by or associated with a virus selected from respiratory syncytial virus, influenza virus, parainfluenza virus, human metapneumovirus, severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV-2), Middle East respiratory syndrome coronavirus (MERS-CoV), human coronavirus OC43, Semliki Forest Virus, a human rhinovirus (HRVs) and human adenovirus (HAdV).

[0066] In certain examples ~~embodiments~~ the viral infection is caused by or associated with a Pneumoviridae virus, for example a Human respiratory syncytial virus (HRSV) (e.g. HRSV-A2, HRSV-B1 or HRSV-S2).

[0067] In certain examples ~~embodiments~~ the viral infection is caused by or associated with a Coronaviridae virus. In certain examples ~~embodiments~~ the viral infection is caused by or associated with a virus is selected from Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. Preferably the viral infection is caused by or associated with a Betacoronavirus. Thus is certain examples ~~embodiments~~ the viral infection is caused by or associated with a virus is selected from severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Middle East respiratory syndrome coronavirus (MERS-CoV), HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1.

[0068] In a particular example ~~embodiment~~ the viral infection is caused by or associated with SARS-CoV-2. This it may be that the viral infection is COVID-19.

[0069] In some examples ~~embodiments~~ the viral infection is caused by or associated with an influenza virus.

[0070] In some examples ~~embodiments~~ the viral infection may be caused by or associated with a virus selected from Flaviviridae (e.g. Zika virus (ZIKV), dengue (e.g. DENV 1−4), West Nile virus (WNV), yellow fever virus (YFV, e.g. yellow fever 17D virus), Japanese encephalitis virus (JEV), Hepatitis C virus (HCV), Filoviridae (e.g. Ebola virus)), Togaviridae (e.g. Alphaviruses such as Chikungunya virus (CHIKV), Sindbis virus and Ross River virus), Herpes (e.g. γ-herpesvirus, Human herpesvirus 8, herpesvirus 1 and herpesvirus 2) and Adenoviridae (e.g. Human adenoviruses (HAdVs)).

[0071] In some examples~~embodiments~~, the viral infection is associated with inflammation. In such examples~~embodiments~~, the treatment may result in a decrease in mucus production and/or secretion,

a decrease in bronchoconstriction, repression of pro-inflammatory cytokines, modulation of the activity of dendritic cells, and/or inhibition of STAT3.

[0072] In some examples~~embodiments~~, the viral infection is associated with a secondary bacterial infection. A secondary bacterial infection may be caused by a bacterium selected from the group consisting of *S. aureus*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes and N. gonorrhoea*.

[0073] The inflammatory disease may be a pulmonary inflammatory disease.

[0074] In some examples~~embodiments~~, the pulmonary inflammatory disease is selected from the group consisting of: asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, interstitial lung disease, sarcoidosis, bronchiolitis obliterans, pneumonitis, and acute respiratory distress syndrome (ARDS).

[0075] The formulation may be administered by inhalation intraorally and/or intranasally. In some examples ~~embodiments~~ the formulation is administered by inhalation intraorally. In certain examples~~embodiments~~, the formulation is administered in the form of an aerosol.

[0076] In some examples ~~embodiments~~ the formulation is administered intranasally. It will be understood that “intranasal” administration means administration into the nasal cavity, i.e. through the nose. Intranasal administration encompasses both administration of the formulation to the nasal mucosa and the upper respiratory tract, and administration of the formulation to the lower respiratory tract (e.g. via inhalation).

[0077] Recent research has identified a gradient of expression levels of the human angiotensin-converting enzyme (ACE)-2, which is targeted by SARS-CoV-2, from the nasal tissues (high expression) and the distal intrapulmonary regions (low expression). This expression pattern was found to be mirrored by a gradient of SARS-CoV-2 infectivity which was high in the nasal epithelium and markedly reduced in the distal lung (bronchioles, alveoli). In light of these findings, it has been suggested that the nasal surfaces may be the dominant initial site of SARS-CoV-2 infection (Hou et al., “SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract”, Cell, 2020). Intranasal administration may therefore be beneficial to subjects suffering from mild COVID-19, or those in the early stages of disease, prior to progression to the later stages of the disease which are characterised by pulmonary inflammation. In some examples~~embodiments~~, subjects whose symptoms include a loss of taste and/or smell, and/or ocular symptoms (e.g. one or more of conjunctival hyperemia, chemosis, epiphora, or increased secretions) may be treated via intranasal administration of the formulation of the present disclosure~~invention~~. Intranasal administration may also be beneficial for treating asymptomatic subjects, for prophylactic treatment of high risk populations as identified herein (e.g. healthcare professionals, or those with underlying

conditions), for treating subjects suspected of having contracted SARS-CoV-2, and/or for treating close contacts of a person with COVID-19.

[0078] In some examples~~embodiments~~, the formulation is administered both intranasally and intraorally (e.g. via inhalation). Thus it may be that a first formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin described herein is administered by inhalation intraorally (e.g. as an aerosol) separately, sequentially or simultaneously with a second formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin described herein, wherein the second formulation is administered intranasally (e.g. as spray). It may be that the first and second formulations are different. It may be that the first and second formulations are the same.

[0079] Subjects with pulmonary viral infections may be prone to coughing when drugs are administered by inhalation. This can make administration of the drug difficult and/or may reduce the dose of drug delivered to the airway and lungs. In certain examples ~~embodiments~~ the subject is administered an antitussive agent prior to or concurrently with the inhaled formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof. Thus it may be that the antitussive agent is selected from codeine, dextromethorphan, hydrocodone, methadone, butorphanol, benzonatate, ethylmorphine, oxeladin, pipazethate, pholcodine, noscapine, butamirate and a local anaesthetic (e.g. lidocaine) prior to or concurrently with the inhaled administration of the niclosamide or a pharmaceutically acceptable salt thereof. Preferably the subject is treated with the antitussive agent prior to administration of the formulation comprising the halogenated salicylanilide (e.g. niclosamide) or pharmaceutically acceptable salt thereof to reduce or eliminate coughing associated with the inhaled administration of the formulation. Thus it may be that the subject is treated with a local anaesthetic prior to or concurrently with the inhaled administration of the formulation comprising the halogenated salicylanilide (e.g. niclosamide) or a pharmaceutically acceptable salt thereof. Suitably the local anaesthetic is administered so as to provide a local anaesthetic effect in the oral cavity and/or airways. Thus it maybe that the local anaesthetic is administered by inhalation or as a gel or liquid to the oral and/or nasal cavity. Suitably the local anaesthetic is lidocaine.

[0080] In some examples~~embodiments~~, the subject is treated with a bronchodilator prior to or concurrently with the formulation comprising the halogenated salicylanilide (e.g. niclosamide) or pharmaceutically acceptable salt thereof. Advantageously, this may help to reduce side effects, such as coughing. Suitable bronchodilators include short-acting β2-adrenergic agonists (e.g. salbutamol, levosalbutamol, pirbuterol, epinephrine, terbutaline or ephedrine),

long-acting β2-adrenergic agonists (e.g. salmeterol, clenbuterol, bambuterol, indacaterol or formoterol), anticholinergics (e.g. tiotropium or ipratropium bromide), and theophylline.

[0081] The halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, may be administered to the subject in a unit dosage of from about 10 mg to about 1000 mg based on the weight of the halogenated salicylanilide or salt thereof, for example from about 100 mg to about 600 mg, preferably about 150 mg to about 500 mg, based on the weight of the halogenated salicylanilide or salt thereof.

[0082] The halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, may be administered to the subject one to five times per day, for example from 1 to 4 times per day, e.g. 2 or 3 times per day.

[0083] In some examples~~embodiments~~, the ocular disease or condition is selected from the group consisting of: an infectious ocular disease, dry eye disease (DED), allergic disease (such as allergic conjunctivitis), blepharitis or an inflammatory eye disease (such as ocular rosacea).

[0084] In some examples~~embodiments~~, the infectious ocular disease is selected from the group consisting of conjunctivitis (including bacterial, fungal and viral conjunctivitis), keratitis (including viral, bacterial, fungal, amoebic and parasitic keratitis), endophthalmitis, blepharitis, sty, uveitis, cellulitis (e.g. bacterial cellulitis) and ocular herpes.

[0085] In some examples ~~embodiments~~ the ocular condition or disease is bacterial conjunctivitis. The bacterial conjunctivitis may be caused by a bacteria selected from the group consisting of *S. aureus* (including MRSA), *S. pneumoniae*, *H. influenzae*, *P. aeruginosa*, *M. catarrhalis* and *N. gonorrhoeae*.

[0086] In some examples ~~embodiments~~ the ocular condition or disease is viral conjunctivitis. The viral conjunctivitis may be caused by adenovirus.

[0087] Wu et al. (Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020 May 01;138(5)) has identified that some patients infected with SARS-CoV-2 exhibit ocular symptoms, and that these symptoms often appeared at the early stages of infection. Accordingly it may be that the liquid formulation is for use in a method of treatment or prevention of a viral infection in a subject (e.g. SARS-CoV-2), the method comprising ocular administration of the liquid formulation to the subject.

[0088] Treatment or prevention of an ocular disease or condition may comprise administering a liquid formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin, for example a formulation

as described herein, topically to one or both eyes. The liquid formulation may comprise an ophthamically acceptable carrier.

[0089] In some examples~~embodiments~~, the liquid formulation is administered to one or both eyes of the subject one to five times per day, for example from 1 to 3 times per day, e.g. 2 times per day.

[0090] Another ~~aspect~~ example of the present disclosure~~invention~~ provides an aerosol of a solution comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin. Thus it may be that the aerosol is an aerosol of a solution comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin. The aerosol may be an aerosol of any of the liquid formulations or solutions as described herein, for example, an aerosol of any of the solutions comprising niclosamide (e.g. niclosamide ethanolamine) and a cyclodextrin (e.g. HP-β-CD) disclosed herein. Suitably the solution is an aqueous solution.

[0091] Also provided is a unit dosage comprising a solution of a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin, wherein the halogenated salicylanilide (e.g. niclosamide) is present in an amount of from about 0.1 mg to about 200 mg, for example from about 0.5 mg to about 100 mg or from about 1 mg to about 50 mg, based on the weight of the halogenated salicylanilide (e.g. niclosamide). The solution may be any of the solutions comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin as described herein. For example, the solution may be any of the solutions comprising niclosamide ethanolamine and a cyclodextrin (e.g. HP-β-CD) as disclosed herein. Suitably the solution is an aqueous solution. The unit dosage is suitably present in a container, for example a vial, blister pack, bottle (e.g. a nasal spray), syringe (e.g. as part of an intranasal delivery device) or reservoir within an inhaler device (e.g. a nebulizer). In examples ~~embodiments~~ wherein the formulation is in the form of a solution, the unit dosage volume administered to the subject may be from 1 to 10 ml, from 2 to 9 ml, from 3 to 8 ml or from 4 to 6 ml. In some examples~~embodiments~~, the unit dosage volume administered to the subject is from 10 µl to 10 ml, from 20 µl to 8 ml, from 30 µl to 6 ml, from 40 µl to 5 ml, from 50 µl to 2 ml, from 100 µl to 1 ml, from 120 µl to 0.8 ml, from 130 µl to 0.7 ml, from 140 µl to 0.6 ml, from 150 µl to 0.5 ml or from 200 µl to 400 µl. In some examples~~embodiments~~, the unit dosage volume administered to the subject is from 100 to 200 µl, from 110 to 190 µl, from 120 to 180 µl, from 130 to 170 µl, from 140 to 160 µl or from 150 to 155 µl. It will be appreciated that the mass of the halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, administered for a given volume will depend on the concentration of the solution. In some examples~~embodiments~~, the halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt

thereof, is present in the solution in an amount of from about 0.01 % to about 10 % by weight. Preferably the solution comprises about 1 % by weight of niclosamide ethanolamine. The volume may be administered one or more times per day, for example once per day, twice per day, three times per day or four times per day. It may be that the volume is administered once or twice per day. It may be that the volume is administered once per day. It may be that the volume is administered twice per day.

[0092] In some examples ~~embodiments~~ wherein a solution of the present disclosure ~~invention~~ is administered intranasally, the volume administered to the subject may be from 50 to 500 µl, from 100 to 400 µl, from 150 to 300 µl or from 200 to 250 µl. It will be appreciated that approximately half of the total volume should be administered to each nostril. In some examples~~embodiments~~, from about 50 to about 150 µl is administered to each nostril (i.e. about 100 to about 300 µl in total). In some examples~~embodiments~~, a volume of about 130 µl-150 µl (e.g. 140 µl) is administered to each nostril (i.e. about 260-300 µl, e.g. 280 µl, in total). Preferably the solution administered intranasally comprises about 1 % by weight of niclosamide ethanolamine. The volume may be administered intranasally one or more times per day, for example once per day, twice per day, three times per day or four times per day. It may be that the volume is administered intranasally once or twice per day. It may be that the volume is administered intranasally once per day. It may be that the volume is administered intranasally twice per day.

[0093] It will further be appreciated that in some examples ~~embodiments~~ wherein a solution of the present disclosure ~~invention~~ is administered both intraorally (i.e. via inhalation) and intranasally, the total volume administered to the subject will be the sum of the volume administered intraorally and the volume administered intranasally. The total volume may be from 10 µl to 10 ml, from 20 µl to 8 ml, from 30 µl to 6 ml, from 40 µl to 5 ml, from 50 µl to 2 ml, from 100 µl to 1 ml, from 150 µl to 0.5 ml or from 200 µl to 400 µl. Preferably the solution administered intranasally comprises about 1 % by weight of niclosamide ethanolamine. As will be appreciated, when the solution is administered both intraorally and intranasally the volume administered intranasally may be the same or different to the volume administered intranasally. Similarly the frequency of the intraoral and intranasal administration may be the same or different. For example, the intraoral and intranasal doses may be administered sequentially (e.g. the intraoral administration followed shortly (e.g. within 10 minutes) by the intranasal administration, or vice versa. In certain examples ~~embodiments~~ the intraoral and intranasal doses may be administered separately (e.g. where the intraoral dosing is separated from the intranasal dosing by more than 10 minutes (e.g. by more than one hour). Also contemplated is substantially simultaneous intraoral and intranasal administration. It may be that the

volume administered intranasally is administered once or twice per day. It may be that the volume administered intraorally is administered once or twice per day.

[0094] As mentioned above, some subjects infected with SARS-CoV-2 present with ocular symptoms, for example conjunctival hyperemia, chemosis, epiphora, or increased ocular secretions. Thus ocular administration (e.g. topically) of a formulation of the present disclosure ~~invention~~ may be effective in preventing or treating SARS-CoV-2. Also contemplated is ocular administration together with intraoral and/or intranasal administration of a formulation of the present disclosure~~invention~~. Accordingly in certain examples ~~embodiments~~ a formulation of the present disclosure ~~invention~~ is administered to the subject topically (e.g. as topically applied eye drops), intranasally and intraorally by inhalation.

[0095] Also provided is a system comprising a container comprising: a formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin; and an inhaler device. The formulation may be a formulation as defined herein.

[0096] Also provided is a kit comprising a container comprising a formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin; and an inhaler device.

[0097] In certain examples ~~embodiments~~ the formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof and a cyclodextrin is present in the system or kit is in the form of a powder, a solution, a suspension, for example any of the formulations described herein. Suitably the formulation is in the form of an aqueous solution.

[0098] In certain examples ~~embodiments~~ the inhaler device of the system or kit is adapted to aerosolize a solution or suspension comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof and a cyclodextrin. Suitably the inhaler device is adapted to deliver the aerosolized solution or suspension intranasally or intraorally to a subject.

[0099] In certain examples ~~embodiments~~ the inhaler device of the system or kit is a nebulizer selected from a jet nebulizer, a vibrating mesh nebulizer, an ultrasonic nebulizer or a pressurised metered dose inhaler (pMDI).

[00100] Also provided is a system comprising a container comprising: a formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin; and an intranasal delivery device. The formulation may be a formulation as defined herein.

[00101] Also provided is a kit comprising a container comprising a formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, and a cyclodextrin; and an intranasal delivery device.

[00102] Further provided is a container containing the formulation comprising a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof and a cyclodextrin. The formulation may be as described herein. In some examples ~~embodiments~~ the formulation comprises an ophthamically acceptable carrier.

[00103] The formulation may be in the form of a liquid. Conveniently, the container may be configured to dispense droplets of the formulation to the eye.

[00104] In a further ~~aspect~~example, there is provided a method of preparing a formulation, the method comprising:

- adding cyclodextrin and/or a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, to a solvent to form a suspension;

- heating (or continuing to heat) the suspension to a temperature of less than 120 °C for a period of time sufficient for the cyclodextrin and/or a halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, to dissolve in the solvent, thereby forming a solution; and

- cooling the solution.

[00105] In some examples~~embodiments~~, both the cyclodextrin and the halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, are added to the solvent prior to heating.

[00106] In some examples~~embodiments~~, the solvent is heated prior to the addition of the cyclodextrin and the halogenated salicylanilide. In such examples~~embodiments~~, after addition of the cyclodextrin and/or halogenated salicylanilide to the solvent to form a suspension, heating may be continued such that the temperature of the suspension is maintained.

[00107] In some examples ~~embodiments~~ the method comprises:

- adding one of cyclodextrin and halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, to the solvent to form a suspension;

- heating (or continuing to heat) the suspension to a temperature of less than 120 °C for a period of time sufficient for the cyclodextrin or halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, to dissolve in the solvent, thereby forming a first solution;

- adding the other of cyclodextrin and halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, to the first solution in the form of a solid;

- heating (or continuing to heat) the first solution to a temperature of less than 120 °C for a period of time sufficient for the solid to dissolve, thereby forming a second solution; and

- cooling the solution.

[00108] In some examples~~embodiments~~, the method comprises:

- adding cyclodextrin to a solvent to form a first suspension, and heating (or continuing to heat) the first suspension to a temperature of less than 120 °C, such as 25 to 100°C, for a period of time sufficient for the cyclodextrin to dissolve in the solvent, thereby forming a first solution;

- adding halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, to a solvent to form a second suspension, and heating (or continuing to heat) the second suspension to a temperature of less than 120 °C, such as 25 to 100°C, for a period of time sufficient for the halogenated salicylanilide (e.g. niclosamide), or a pharmaceutically acceptable salt thereof, to dissolve in the solvent, thereby forming a second solution;

- adding the first solution to the second solution to form a mixture; and

- cooling the mixture.

[00109] In some examples ~~embodiments~~ in any of the methods described herein the pH of the solvent, solution or suspension is adjusted to a pH of 7 or greater (e.g. 8 to 12). A high pH has been found to aid formation of an inclusion complex between the cyclodextrin and the niclosamide or a pharmaceutically acceptable salt thereof. In certain examples ~~embodiments~~ the pH of the solvent, solution or suspension is adjusted to a pH of 8 or greater.

[00110] In some examples ~~embodiments~~ the pH is adjusted to a pH of 7 or greater (e.g. a pH of 8 or greater, such as a pH of 8 to 12) prior to the addition of the halogenated salicylanilide. The pH may be adjusted by adding a base (e.g. NaOH).

[00111] In some examples ~~embodiments~~ in any of the methods described herein the suspension further comprises a water-soluble polymer (e.g. PVP). The presence of a polymer such as PVP has been found to enhance the an inclusion complex between the cyclodextrin and the niclosamide or a pharmaceutically acceptable salt thereof and enables high concentration aqueous solutions of niclosamide, or a pharmaceutically acceptable salt thereof to be prepared. Thus, in some examples~~embodiments~~, the method comprises adding a water-soluble polymer (e.g. PVP) to the solution or suspension. In some examples~~embodiments~~, the water-soluble polymer is added to the second solution.

[00112] In some examples~~embodiments~~, the method comprises heating (or continuing to heat) the mixture at a temperature of less than 120 °C, after adding the first solution to the second solution, prior to cooling. Heating may be carried out to a temperature of from 25 to around 120, e.g. 50 to 120 °C.

[00113] In some examples~~embodiments~~, cooling is carried out to a temperature of from 10 to 40 °C.

[00114] In some examples ~~embodiments~~ the solvent is an aqueous solvent. Suitably the solvent is substantially free from volatile organic solvents (e.g. ethanol). Preferably the solvent is water.

[00115] In preferred examples ~~embodiments~~ of the methods described herein the halogenated salicylanilide is niclosamide ethanolamine.

[00116] ~~Embodiments~~ Examples of the present disclosure~~invention~~ will now be described by way of example and with reference to the accompanying Figures, in which:

Figure 1 shows graphs showing the epithelial lining fluid (ELF) concentration of niclosamide free base following pulmonary administration in sheep compared to systemic exposure of highest human oral dose, relative to IC90 against SARS-CoV-2. (**A**) Mean ELF concentration of niclosamide over time following pulmonary administration of a formulation of the present disclosure ~~invention~~ (± SEM); (**B**) Comparison of mean Cmax levels of niclosamide following pulmonary administration of a formulation of the present disclosure~~invention~~ in ELF to systemic Cmax following a 2 g/day oral dose in humans (Data of Andrews et al. 1983, *Pharmacology & therapeutics,* 19(2), 245–295 (healthy volunteers) and Burock et al. 2018, BMC Cancer, 18(1): 297 (colorectal cancer patients) combined in “2000 mg single/qd” column);

Figure 2 shows plots showing the pharmacokinetic profile of niclosamide ethanolamine per cohort in the phase 1 clinical trial described in Example 13;

Figure 3 is a comparison of systemic exposure (Cmax; mean ± SEM) of niclosamide administered orally (as reported in the literature) versus inhalation of a formulation according to the present disclosure ~~invention~~ in humans. No mean for “2000 mg, single” column generated as only range of Cmax reported in literature. Data for 500-1000 mg obtained from Schweizer et al., 2018, PLoS ONE.;13(6): e0198389. Data for 2000 mg obtained from Andrews et al. 1983 and Burock et al. 2018 (as above);

Figure 4 shows a correlation plot of systemic exposure (Cmax-, mean ±) of human versus sheep study;

Figure 5 shows the Inhibition of SARS-CoV-2 replication in VeroE6 cells (Fig. 5A) and Caco-2 cells (Fig. 5B) by niclosamide ethanolamine salt;

Figure 6 is a graph showing that Niclosamide ethanolamine salt inhibits replication of several variants of SARS-CoV-2;

Figure 7 shows the effect of Niclosamide ethanolamine salt on apical viral infectious titer TCID50 (Fig. 7A) and intracellular RNA levels (Fig. 7B) of SARS-CoV-2 in a trans-well system of infection. N= 2. Mean with 95% levels shown for Fig. 7A, and Mean ± SD for Fig. 7B. * $p < 0.05$, Ordinary one-way ANOVA with Dunetts' multiple comparison test; and

Figure 8 shows the clinical score of SARS-COV-2 infected K18-hACE2 transgenic mice on Day 6 post infection with a formulation according to the present disclosure ~~invention~~ compared to saline. N=5 for formulation and N=6 for saline. ** = $p < 0.01$ (Mann Whitney Test).

DETAILED DESCRIPTION

Definitions

[00117] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[00118] References to "formulation of the invention", "formulations of the invention" "solution of the invention" refer to any of the formulations described herein comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and a cyclodextrin. A "solution of the invention" refers to a formulation of the invention wherein the halogenated salicylanilide or pharmaceutically acceptable salt thereof is dissolved in the formulation.

[00119] The terms "treating" or "treatment" refers to any indicia of success in the treatment or amelioration of a disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the pathology or condition more tolerable to the subject; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving the physical or mental well-being of the subject. For example, in relation to the treatment of the infectious, inflammatory and ocular diseases disclosed herein the treatment may include one or more of the following: Reduce or eliminate the virus; prevent or reduce viral replication; reduce or eliminate transmission of the infection; reduce or eliminate fever; reduce or eliminate flu-like symptoms, reduce or eliminate coughing, reduce or eliminate muscle and/or joint pain; improve respiratory status of the subject (e.g. increasing blood oxygen saturation; reducing or eliminating the requirement for oxygen therapy); an improvement in the NEWS2 score; the prevention or treatment of acute respiratory distress syndrome, e.g. associated with the viral infection; the treatment or prevention of pneumonia associated with the viral infection; the treatment or prevention of viral pneumonia; the treatment or prevention of bacterial pneumonia associated with a viral infection or an inflammatory pulmonary disease; reducing or eliminating pulmonary

Claims

1. A formulation comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and a cyclodextrin.

2. The formulation according to claim 1, wherein the halogenated salicylanilide is selected from the group consisting of niclosamide, closantel, oxyclozanide and rafoxanide, or a pharmaceutically acceptable salt thereof.

3.The formulation according to claim 1 or claim 2, wherein the halogenated salicylanilide is niclosamide, or a pharmaceutically acceptable salt thereof.

4. The formulation according to claim 3, wherein the pharmaceutically acceptable salt is niclosamide ethanolamine.

5. The formulation according to any one of claims 1 to 4, wherein the formulation is in the form of a solid, or
wherein the formulation is in the form of a solution, suspension or dispersion of the halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and the cyclodextrin in a pharmaceutically acceptable solvent; preferably wherein the solvent comprises water.

6. The formulation according to any preceding claim, wherein the cyclodextrin comprises β-cyclodextrin or a derivative thereof, optionally wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin (HP-β-CD).

7. The formulation according to any preceding claim, wherein the halogenated salicylanilide, or the pharmaceutically acceptable salt thereof, is present in the formulation in an amount of from 0.05 to 10 % by weight, optionally from 0.5 to 1 % by weight, based on the weight of the formulation.

8. The formulation according to any preceding claim, wherein the formulation is a liquid formulation and the cyclodextrin is present in the formulation in an amount of from 1 to 25 % by weight, e.g. from 10 to 15 % by weight, based on the weight of the liquid formulation.

9. The formulation according to any preceding claim, further comprising at least one polymer, optionally wherein the polymer is selected from the group consisting of polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA), polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA),

hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose acetate succinate (HPMC-AS), poloxamers, hydroxypropylmethylcellulose (HPMC), and any combination thereof, optionally wherein the polymer comprises PVP.

10. A formulation comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and a cyclodextrin, for use as a medicament, wherein the formulation is as defined by any one of claims 1 to 9.

11. Use of a~~A~~ formulation comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and a cyclodextrin, ~~for use~~ in the manufacture of a medicament for the treatment or prevention of an infectious disease or an inflammatory disease in a subject in need thereof, wherein the formulation is as defined by any one of claims 1 to 9.

12. The ~~formulation for~~ use according to claim 11, wherein the infectious disease is a viral infection, optionally wherein the viral infection is caused by or associated with a virus selected from respiratory syncytial virus, influenza virus, parainfluenza virus, human metapneumovirus, severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV-2), Middle East respiratory syndrome coronavirus (MERS-CoV), a human rhinovirus (HRVs) and human adenovirus (HAdV).

13. The ~~formulation for~~ use according to claim 11, wherein the inflammatory disease is a pulmonary inflammatory disease selected from the group consisting of: asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, interstitial lung disease, sarcoidosis, bronchiolitis obliterans, pneumonitis, acute respiratory distress syndrome (ARDS), bronchiectasis, cystic fibrosis, idiopathic pulmonary fibrosis, radiation induced fibrosis, silicosis, asbestos induced pulmonary or pleural fibrosis, acute lung injury, usual interstitial pneumonia (UIP), Chronic lymphocytic leukemia (CLL)-associated fibrosis, Hamman-Rich syndrome, Caplan syndrome, coal worker's pneumoconiosis, cryptogenic fibrosing alveolitis, obliterative bronchiolitis, chronic bronchitis, emphysema, Wegner's granulamatosis, lung scleroderma, silicosis, asbestos induced pulmonary and/or pleural fibrosis.

14. The ~~formulation for~~ use according to any one of claims 11 to 13, wherein ~~said use comprises administering~~ the formulation is to be administered by inhalation intraorally and/or intranasally, optionally wherein the formulation is to be administered by inhalation intraorally.

15. Use of a~~A~~ formulation comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and a cyclodextrin, ~~for use~~ in the manufacture of a medicament for the treatment or prevention of an infectious ocular disease or an inflammatory ocular disease in a subject, wherein the formulation is as defined by any one of claims 1 to 9.

16. The ~~formulation for~~ use according to claim 15, wherein the infectious ocular disease is selected from the group consisting of conjunctivitis (including bacterial, fungal and viral conjunctivitis), keratitis (including viral, bacterial, fungal and amoebic keratitis), endophthalmitis, blepharitis, sty, uveitis, cellulitis (e.g. bacterial cellulitis), ocular gonorrhoea and ocular herpes.

17. The ~~formulation for~~ use according to claim 15, wherein the inflammatory ocular disease is elected from dry eye disorder (DED), ocular rosacea, uveitis (e.g. Birdshot retinochoroidopathy), severe conjunctivitis, diabetic retinopathy, multifocal choroiditis with panuveitis, serpiginous choroidopathy, scleritis, an eye inflammation associated with allergy (such as allergic conjunctivitis), and an eye inflammation associated with an autoimmune disorder (e.g. mucous membrane pempigoid, eye inflammation associated with infection, retinitis pigmentosa, ankylosing spondylitis, Behcet's syndrome, dermatomyositis, Graves' disease, juvenile rheumatoid arthritis, multiple sclerosis, psoriatic arthritis, blepharitis, Reiter's syndrome, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, and Wegener's granulatomatosis).

18. An aerosol of a solution comprising a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, and cyclodextrin.

19. An aerosol according to claim 18, wherein the solution comprises niclosamide ethanolamine.

20. The aerosol according to claims 18 or claim 19, wherein the cyclodextrin is β-cyclodextrin or a derivative thereof, optionally wherein the cyclodextrin comprises hydroxypropyl-β-cyclodextrin (HP-β-CD).

21. The aerosol according to any one of claims 18 to 20, wherein the solution further comprises at least one polymer, optionally wherein the polymer is selected from the group consisting of polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA), polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA), hydroxypropylcellulose (HPC), poloxamers,

hydroxypropylmethylcellulose (HPMC), and any combination thereof, optionally wherein the polymer comprises PVP.

22. Use of t~~T~~he aerosol according to any one of claims 18 to 21, ~~for use~~ in the manufacture of a medicament for the treatment or prevention of an infectious disease or an inflammatory disease in a subject, optionally a pulmonary infectious or inflammatory disease, wherein ~~said use comprises administration of~~ the aerosol is to be administered to the subject by inhalation.

23. The ~~aerosol for~~ use according to claim 22, wherein the infectious disease is a viral infection.

24. A system comprising:

- a formulation as defined by any one of claims 1 to 9; and
- an inhaler device and/or an intranasal delivery device.

25. A method of preparing a formulation, the method comprising:

- adding cyclodextrin and/or a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, to a solvent to form a suspension;
- heating the suspension for a period of time sufficient for the cyclodextrin and/or a halogenated salicylanilide, or a pharmaceutically acceptable salt thereof, to dissolve in the solvent, thereby forming a solution;
- optionally, adding one or more polymers to the suspension or the solution, optionally wherein the polymer comprises PVP;
- optionally, raising the pH of the suspension or solution, optionally wherein the pH is raised to a pH of 8-13; and
- cooling the solution.

26. A formulation according to any one of claims 1 to 9, or an aerosol according to any one of claims 18 to 21, for use in therapy.