METHODS OF TREATING CHRONIC INFLAMMATORY DISEASES

BACKGROUND OF THE INVENTION

[0001] Chronic inflammatory disease(s) (CID) underpins the pathological condition characterized by chronic inflammation, defined as a prolonged and persistent pro-inflammatory state (1). CID includes many common and uncommon CID such as respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease, pneumonitis, and pulmonary fibrosis) (2), ocular diseases (e.g., keratitis and age-related macular degeneration) (3), autoimmune diseases (4), nephropathy (5), neurodegenerative diseases (e.g., Alzheimer's disease, stroke, Parkinson's disease, and multiple sclerosis) (6), cardiovascular diseases (e.g., atherosclerosis, arteriosclerosis, and myocarditis) (7), metabolic disorders (e.g., diabetes and obesity) (8), musculoskeletal diseases (e.g., rheumatoid arthritis and osteoporosis) (9, 10), periodontal diseases (e.g., pulpitis and periodontitis) (11), digestive diseases (e.g., non-alcoholic fatty liver disease, gastroenteritis, and chronic inflammatory bowel disease) (12), and skin disorders (e.g., psoriasis and atopic dermatitis) (13, 14).

[0002] An epidemiological study showed that CID is a leading cause of death throughout the world and has been increasing over the last three decades. It has been estimated that by 2030, 171 million people will be affected by CID in the United States (15). There are various types of anti-inflammatory drugs to treat inflammation, such as aspirin, antihistamines, COX-2 inhibitors, corticosteroid, and nonsteroidal anti-inflammatory drugs (NSAIDs). However, there are limitations for long term administration of such existing drugs due to side effects and temporal efficacy.

BRIEF SUMMARY

[0002a] In one aspect of the present disclosure, there is provided a use of calcium lactate in the manufacture of a medicament for treating Alzheimer's disease, Parkinson's disease, atherosclerosis, and/or stroke.

[0002b] In another aspect of the present disclosure, there is provided a use of calcium lactate in the manufacture of a medicament for treating multiple sclerosis, age-related macular

degeneration, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or rheumatoid arthritis.

[0002c] In a further aspect of the present disclosure, there is provided a use of calcium lactate in the manufacture of a medicament for treating pulpitis and/or periodontitis.

[0002d] In another aspect of the present disclosure, there is provided a use of calcium lactate in the manufacture of a medicament for treating inflammatory bowel disease (IBD) or Crohn's disease or ulcerative colitis.

[0002e] In a further aspect of the present disclosure, there is provided a use of calcium lactate in the manufacture of a medicament for treating spinal cord injury, cerebral hemorrhage, myocardial infarction, keratitis, and/or diabetic retinopathy.

[0003] Disclosed herein is a method of treating a chronic inflammatory disease, the method comprising administering to a subject in need thereof a therapeutically effective amount of calcium lactate.

[0004] Disclosed herein is a method of treating Alzheimer's disease, Parkinson's disease, atherosclerosis, and/or stroke, the method comprising administering to a subject in need thereof a therapeutically effective amount of calcium lactate.

[0005] Also disclosed is a method of treating multiple sclerosis, age-related macular degeneration, nonalcoholic fatty liver disease (NAFLD), and/or rheumatoid arthritis, the

method comprising administering to a subject in need thereof a therapeutically effective amount of calcium lactate. In some examples, the method is for treating NAFLD and the NAFLD is nonalcoholic steatohepatitis (NASH).

[0006] Also disclosed is a method of treating pulpitis and/or periodontitis, the method comprising administering to a subject in need thereof a therapeutically effective amount of calcium lactate.

[0007] Further disclosed is a method of treating inflammatory bowel disease (IBD), the method comprising administering to a subject in need thereof a therapeutically effective amount of calcium lactate. In some examples, the IBD is Crohn's disease or ulcerative colitis.

[0008] Further disclosed is a method of treating spinal cord injury, cerebral hemorrhage, myocardial infarction, keratitis, and/or diabetic retinopathy, the method comprising administering to a subject in need thereof a therapeutically effective amount of calcium lactate.

[0009] Disclosed herein is a method of treating asthma, pulmonary fibrosis, obesity, gastroenteritis, chronic inflammatory bowel disease, and/or atopic dermatitis, the method comprising administering to a subject in need thereof a therapeutically effective amount of calcium lactate. Also disclosed herein is a method of treating chronic obstructive pulmonary disease, pneumonitis, keratitis, atherosclerosis, arteriosclerosis, myocarditis, diabetes, rheumatoid arthritis, pulpitis, periodontitis, and/or psoriasis, the method comprising administering to a subject in need thereof a therapeutically effective amount of calcium lactate. Also disclosed herein is a method of treating Alzheimer's disease, stroke, Parkinson's disease, multiple sclerosis, age-related macular degeneration, non-alcoholic fatty liver disease, sepsis, and/or osteoporosis, the method comprising administering to a subject in need thereof a therapeutically effective amount of calcium lactate.

[0010] In some examples, the calcium lactate is administered in a pharmaceutical composition comprising a pharmaceutically acceptable carrier, excipient, and/or diluent. In some examples, the pharmaceutical composition is formulated into liquid, powder, aerosol, injection, fluid transfusion, patch, capsule, pill, tablet, depot, or suppository.

[0011] In some examples, the pharmaceutical composition comprises a therapeutically effective amount of calcium lactate as an active agent and a pharmaceutically acceptable polysaccharide, polymer, lipid, or combinations thereof. In some examples, the pharmaceutical composition comprises the calcium lactate and the polysaccharide. In some examples, a weight ratio of the calcium lactate to the polysaccharide is 1:<0.2 to 1:5. In some examples, a weight ratio of the calcium lactate to the polysaccharide is 1:<0.2. In some examples, a weight ratio of the calcium lactate to the polysaccharide is 1:0.2 to 1:5.

[0012] In some examples, the pharmaceutical composition further comprises a polymer and/or lipid. In some examples, the pharmaceutical composition further comprises the polymer and lipid, wherein the weight ratio of the polymer to the lipid is 1:0.1 to 1:50. In some examples, the weight ratio of the calcium lactate to the polymer and/or lipid is at least 1:5. In some examples, a weight ratio of the calcium lactate to the polymer and/or lipid is 1:5 to 1:30.

[0013] In some examples, the pharmaceutical composition comprises the calcium lactate and the polymer and/or lipid. In some examples, the pharmaceutical composition comprises the polymer and lipid, wherein the weight ratio of the polymer to the lipid is 1:0.1 to 1:50. In some examples, a weight ratio of the calcium lactate to the polymer and/or lipid is at least 1:5. In some examples, the weight ratio of the calcium lactate to the polymer and/or lipid is 1:5 to 1:30.

[0014] In some examples, the composition is short-acting. In some examples, the composition is long-acting. In some examples, the composition is an injectable composition.

[0015] In some examples, the polysaccharide is a cellulose derivative, pectin, hyaluronic acid, starch, guar gum, chitosan, gelatin, collagen, alginate, alginic acid or combinations thereof.

[0016] In some examples, the polymer is a poloxamer, polyvinylpyrrolidone, polyethylene glycol (PEG), polyglycolic lactic acid (PLGA), or combinations thereof.

[0017] In some examples, the lipid is a mono- or tri-fatty acid glycerin ester or polyethylene glycol, polyethylene glycol esters of vegetable oils, fatty acid propylene glycol esters, sesame oil, soybean oil, castor oil, corn oil, palm oil, peanut oil, cacao oil, cottonseed oil, sunflower seed oil, safflower oil, almond oil, olive oil, hydrogenated oil, oleic acid, linolenic acid, linoleic acid, palmitic acid, palmitoleic acid, arachadonic acid, myristic acid, capric acid, caprylic acid, lauric acid, stearic acid, ethyl oleate, isopropyl palmitate, octyldodecyl myristate, cetyl palmitate, lauryl alcohol, oleyl alcohol, cetyl alcohol, stearyl alcohol, or combinations thereof.

[0018] In some examples, upon placement of the pharmaceutical composition in an in vitro dissolution test comprising an elution test method at 300 rpm in 200 ml aqueous medium having a pH of 6.8 at 37°C using a nylon filter having a pore size of 45 μm, at least about 40% of the active agent is released after 6 hours.

[0019] In some examples, upon placement of the pharmaceutical composition in an in vitro dissolution test comprising an elution test method at 300 rpm in 200 ml aqueous medium

having a pH of 6.8 at 37°C using a nylon filter having a pore size of 45 μm, at least about 60% of the active agent is released after 12 hours.

[0020] In some examples, upon placement of the pharmaceutical composition in an in vitro dissolution test comprising an elution test method at 300 rpm in 200 ml aqueous medium having a pH of 6.8 at 37°C using a nylon filter having a pore size of 45 μm, at least about 80% of the active agent is released after 24 hours.

[0021] In some examples, upon placement of the pharmaceutical composition in an in vitro dissolution test comprising an elution test method at 300 rpm in 200 ml aqueous medium having a pH of 6.8 at 37°C using a nylon filter having a pore size of 45 μm, at least about 90% of the active agent is released after 48 hours.

[0022] In some examples, wherein upon placement of the pharmaceutical composition in an in vitro dissolution test comprising an elution test method at 300 rpm in 200 ml aqueous medium having a pH of 6.8 at 37°C using a nylon filter having a pore size of 45 μm, less than about 40% of the active agent is released after 24 hours.

[0023] In some examples, upon placement of the pharmaceutical composition in an in vitro dissolution test comprising an elution test method at 300 rpm in 200 ml aqueous medium having a pH of 6.8 at 37°C using a nylon filter having a pore size of 45 μm, less than about 60% of the active agent is released after 48 hours.

[0024] In some examples, upon placement of the pharmaceutical composition in an in vitro dissolution test comprising an elution test method at 300 rpm in 200 ml aqueous medium having a pH of 6.8 at 37°C using a nylon filter having a pore size of 45 μm, less than about 80% of the active agent is released after 72 hours.

[0025] In some examples, upon placement of the pharmaceutical composition in an in vitro dissolution test comprising an elution test method at 300 rpm in 200 ml aqueous medium having a pH of 6.8 at 37°C using a nylon filter having a pore size of 45 μm, less than about 90% of the active agent is released after 144 hours.

[0026] In some examples, the pharmaceutical composition is contained in a sterile glass or polyolefin container.

[0027] In some examples, the calcium lactate is coated with a pharmaceutically acceptable enteric coating. In some examples, the enteric coating comprises hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), shellac, polymer of methacrylic acid and an ester thereof, or combinations thereof. In some examples, the weight ratio of the calcium lactate to the enteric coating is 10:0.5 to 1:1.5. In some examples, in an in vitro dissolution test comprising a USP Paddle method at a paddle speed of 50 rpm at 37°C, when the composition is placed in 0.1 HCl for 120 minutes followed by adjusting to pH 6.8 with phosphate buffer, less than about 20% of the active agent is released after 30 minutes. In some examples, in an in vitro dissolution test comprising a USP Paddle method

at a paddle speed of 50 rpm at 37°C, when the composition is placed in 0.1 N HCl for 120 minutes followed by adjusting to pH 6.8 with phosphate buffer, less than 30% of the active agent is released after 60 minutes. In some examples, in an in vitro dissolution test comprising a USP Paddle method at a paddle speed of 50 rpm at 37°C, when the composition is placed in 0.1 N HCl for 120 minutes followed by adjusting to pH 6.8 with phosphate buffer, less than 50% of the active agent is released after 120 minutes. In some examples, in an in vitro dissolution test comprising a USP Paddle method at a paddle speed of 50 rpm at 37°C, when the composition is placed in 0.1 N HCl for 120 minutes followed by adjusting to pH 6.8 with phosphate buffer, less than 10% of the active agent is released after 120 minutes.

[0028] In some examples, the calcium lactate is provided in a food or nutrient composition comprising calcium lactate. In some examples, the food or nutrient composition is an injectable nutritional supplement.

BRIEF DESCRIPTION OF THE FIGURES

[0029] **FIG. 1.** Human leukemic monocyte in vitro experiment. Western blot results indicated that inflammatory factor (NF-κb) was decreased by 2.5 mM calcium lactate treatment in THP-1 cells (human leukemic monocyte) under hypoxia condition.

[0030] **FIG. 2.** In vitro experiment of human leukemic monocytes differentiated into macrophages. Western blot results indicated that inflammatory factor (NF-κb) was decreased by 2.5 mM calcium lactate treatment in differentiated THP-1 cells with PMA (phorbol-12-myristate-13-acetate) (M0 macrophage) under normoxia and hypoxia conditions.

[0031] **FIG. 3.** Western blot results indicated that inflammatory factor (NF-κb) was decreased by 2.5 mM calcium lactate treatment in differentiated THP-1 cells with interferon gamma (IFN-γ) and Lipopolysaccharide (LPS) (M1 macrophage) under normoxia and hypoxia conditions.

[0032] **FIG. 4.** Western blot results indicated that inflammatory factor (NF-κb) was decreased by 2.5 mM calcium lactate treatment in differentiated THP-1 cells with interleukin-4 (IL-4) and interleukin-10 (IL-10) (M2 macrophage) under normoxia and hypoxia conditions.

WHAT IS CLAIMED IS

1. Use of calcium lactate in the manufacture of a medicament for treating Alzheimer's disease, Parkinson's disease, atherosclerosis, and/or stroke.

2. Use of calcium lactate in the manufacture of a medicament for treating multiple sclerosis, age-related macular degeneration, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or rheumatoid arthritis.

3. Use of calcium lactate in the manufacture of a medicament for treating pulpitis and/or periodontitis.

4. Use of calcium lactate in the manufacture of a medicament for treating inflammatory bowel disease (IBD) or Crohn's disease or ulcerative colitis.

5. Use of calcium lactate in the manufacture of a medicament for treating spinal cord injury, cerebral hemorrhage, myocardial infarction, keratitis, and/or diabetic retinopathy.

6. The use of any one of claims 1-5, wherein the medicament is a pharmaceutical composition comprising a pharmaceutically acceptable carrier, excipient, or diluent.

7. The use of any one of claims 1-5, wherein the medicament is formulated into liquid, powder, aerosol, injection, fluid transfusion, patch, capsule, pill, tablet, depot, or suppository.

8. The use of any one of claims 1-5, wherein the medicament comprises a therapeutically effective amount of calcium lactate as an active agent and a pharmaceutically acceptable polysaccharide, polymer, lipid, or combinations thereof.

9. The use of claim 8, wherein the pharmaceutical composition comprises the calcium lactate and the polysaccharide.

10. The use of claim 9, wherein a weight ratio of the calcium lactate to the polysaccharide is 1:<0.2 to 1:5.

11. The use of any one of claims 9, wherein the pharmaceutical composition further comprises a polymer and/or lipid.

12. The use of claim 11, wherein the pharmaceutical composition further comprises the polymer and lipid, wherein the weight ratio of the polymer to the lipid is 1:0.1 to 1:50.

13. The use of any one of claims 8-12, wherein the medicament or pharmaceutical composition comprises the polysaccharide that is a cellulose derivative, pectin, hyaluronic acid, starch, guar gum, chitosan, gelatin, collagen, alginate, alginic acid or combinations thereof.

14. The use of any one of claims 8-13, wherein the medicament or pharmaceutical composition comprises the polymer that is a poloxamer, polyvinylpyrrolidone, polyethylene glycol (PEG), polyglycolic lactic acid (PLGA), or combinations thereof.

15. The use of any one of claims 8-14, wherein the medicament or pharmaceutical composition comprises the lipid that is a mono- or tri-fatty acid glycerin ester or polyethylene glycol, polyethylene glycol esters of vegetable oils, fatty acid propylene glycol esters, sesame oil, soybean oil, castor oil, corn oil, palm oil, peanut oil, cacao oil, cottonseed oil, sunflower seed oil, safflower oil, almond oil, olive oil, hydrogenated oil, oleic acid, linolenic acid, linoleic acid, palmitic acid, palmitoleic acid, arachadonic acid, myristic acid, capric acid, caprylic acid, lauric acid, stearic acid, ethyl oleate, isopropyl palmitate, octyldodecyl myristate, cetyl palmitate, lauryl alcohol, oleyl alcohol, cetyl alcohol, stearyl alcohol, or combinations thereof.

16. The use of any one of claims 8-15, wherein the medicament or pharmaceutical composition is contained in a sterile glass or polyolefin container.

17. The use of any one of claims 1-8, wherein the calcium lactate is coated with a pharmaceutically acceptable enteric coating.

18. The use of claim 17, wherein the enteric coating comprises hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), shellac, polymer of methacrylic acid and an ester thereof, or combinations thereof.

19. The use of any one of claims 17-18, wherein the weight ratio of the calcium lactate to the enteric coating is 10:0.5 to 1:1.5.