[0019] Figure 16 shows mean skin blister fluid concentration of total DGLA (ng/mL, linear plot), by dose cohort (Multiple-dose, PK Population).

[0020] Figure 17 shows mean skin blister fluid concentration of total DGLA (ng/mL, log-linear plot), by dose cohort (Multiple-dose, PK Population)

[0021] Figure 18 shows mean free DGLA concentration (ng/mL, linear plot) in plasma and skin blister fluid, by dose cohort (Multiple-dose, PK Population).

[0022] Figure 19 shows mean free DGLA concentration (ng/mL, log-linear plot) in plasma and skin blister fluid, by dose cohort (Multiple-dose, PK Population).

[0023] Figure 20 shows mean total DGLA concentration (ng/mL, linear plot) in plasma and skin blister fluid, by dose cohort (Multiple-dose, PK Population).

[0024] Figure 21 shows mean total DGLA concentration (ng/mL, log-linear plot) in plasma and skin blister fluid, by dose cohort (Multiple-dose, PK Population).

[0025] Figure 22 shows mean plasma dihydrotestosterone concentration (ng/mL, linear plot), by dose cohort (Multiple-dose, PK Population).

[0026] Figure 23 shows mean plasma dihydrotestosterone concentration (ng/mL, log-linear plot), by dose cohort (Multiple-dose, PK Population).

SUMMARY

[0027] The present disclosure describes orally deliverable pharmaceutical compositions comprising DGLA and to methods of using same to treat a variety of conditions and disorders. In one aspect, the present invention refers to a pharmaceutical composition comprising dihomo gamma linolenic acid (DGLA) or a derivative thereof encapsulated in a capsule shell, wherein the composition comprises at least about 80% DGLA by weight of total fatty acids and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid. In another aspect, the present invention refers to a pharmaceutical composition comprising dihomo gamma linolenic acid (DGLA) or a derivative thereof encapsulated in a capsule shell comprising gelatin and glycerol, wherein the composition comprises at least about 80% DGLA by weight of total fatty acids and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid. In yet another aspect, the present invention refers to use of

apharmaceutical composition comprising dihomo gamma linolenic acid (DGLA) or a derivative thereof in the manufacture of a medicament for treating a skin disease or disorder, wherein the composition comprises at least about 80% DGLA by weight of total fatty acids and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid. In a further aspect, there is disclosed use of a pharmaceutical composition comprising dihomo gamma linolenic acid (DGLA) or a derivative thereof encapsulated in a capsule shell comprising gelatin, d-sorbitol and 1,4-sorbitan sugar alcohols in the manufacture of a medicament for increasing skin DGLA levels or treating a skin disease, wherein the composition comprises at least about 80% DGLA by weight of total fatty acids and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid. In yet another aspect, there is disclosed a pharmaceutical composition comprising 200 mg to about 1 g of a composition encapsulated in a capsule shell, wherein the composition comprises not less than 95% by weight dihomo gamma linolenic acid (DGLA), not more than 5% of any individual fatty acid selected from 20:2ω6, 20:3ω3, 20:4ω6, 20:4ω3 and 20:5ω3, and not more than 2% by weight unidentified related substances, wherein the composition comprises at least about 80% DGLA by weight of total fatty acids and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid. In a further aspect, there is disclosed Use of a pharmaceutical composition comprising at least about 80% dihomo gamma linolenic acid (DGLA) or a derivative thereof by weight of total fatty acids in the composition, and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid, in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof, wherein the disease or disorder is selected from: skin disorders and diseases, including acne vulgaris, acne rosacea, atopic dermatitis, psoriasis, pruritus/itch, radiation protection, dry skin, smooth skin, healthy skin, anti-aging, and photoprotection; urinary disorders and diseases including bladder cancer, cystocele, hematuria, interstitial cystitis, neurogenic bladder, Peyronie's disease, prostate disease, incontinence, urinary tract infection and vasicoureteral reflux; renal disease and disorders including kidney failure, acute kidney injury, chronic kidney disease, and polycystic kidney disease; rheumatic disease including ankylosing spondylitis, fibromyalgia, gout, infectious arthritis, lupus, osteoarthritis, polymyalgia rheumatic, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, sclerodoma; respiratory disorders including inflammatory lung

disease, respiratory tract infections, pleural cavity disease, pulmonary vascular disease, pneumonia, pulmonary embolism, and lung cancer; and cardiovascular disorders including acute cardiac ischemic events, acute myocardial infarction, angina, arrhythmia, atrial fibrulation, atherosclerosis, arterial fibrillation, cardiac insufficiency, cardiovascular disease, chronic heart failure, chronic stable angina, congestive heart failure, coronary artery disease, coronary heart disease, deep vein thrombosis, diabetes, diabetes mellitus, diabetic neuropathy, diastolic dysfunction in subjects with diabetes mellitus, edema, essential hypertension, eventual pulmonary embolism, fatty liver disease, heart disease, heart failure, homozygous familial hypercholesterolemia (HoFH), homozygous familial sitosterolemia, hypercholesterolemia, hyperlipidemia, hypertension, hypertriglyceridemia, metabolic syndrome, mixed dyslipidemia, moderate to mild heart failure, myocardial infarction, obesity management, paroxysmal atrial/arterial fibrillation/fibrulation/flutter, paroxysmal supraventricular tachycardias (PSVT), particularly severe or rapid onset edema, platelet aggregation, primary hypercholesterolemia, primary hyperlipidemia, pulmonary arterial hypertension, pulmonary hypertension, recurrent hemodynamically unstable ventricular tachycardia (VT), recurrent ventricular arrhythmias, recurrent ventricular fibrillation (VF), ruptured aneurysm, sitisterolemia, stroke, supraventricular tachycardia, symptomatic atrial fibrillation/flutter, tachycardia, type-II diabetes, vascular disease, venous thromboembolism, and ventricular arrhythmias. In yet another aspect, there is disclosed a pharmaceutical composition as disclosed herein for use in treating of skin disorders and diseases, including acne vulgaris, acne rosacea, atopic dermatitis, psoriasis, pruritus/itch, radiation protection, dry skin, smooth skin, healthy skin, anti-aging, and photoprotection; urinary disorders and diseases including bladder cancer, cystocele, hematuria, interstitial cystitis, neurogenic bladder, Peyronie's disease, prostate disease, incontinence, urinary tract infection and vasicoureteral reflux; renal disease and disorders including kidney failure, acute kidney injury, chronic kidney disease, and polycystic kidney disease; rheumatic disease including ankylosing spondylitis, fibromyalgia, gout, infectious arthritis, lupus, osteoarthritis, polymyalgia rheumatic, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, sclerodoma; respiratory disorders including inflammatory lung disease, respiratory tract infections, pleural cavity disease, pulmonary vascular disease, pneumonia, pulmonary embolism, and lung cancer; and cardiovascular disorders including acute cardiac ischemic events, acute myocardial infarction, angina, arrhythmia, atrial fibrulation, atherosclerosis, arterial fibrillation, cardiac insufficiency,

cardiovascular disease, chronic heart failure, chronic stable angina, congestive heart failure, coronary artery disease, coronary heart disease, deep vein thrombosis, diabetes, diabetes mellitus, diabetic neuropathy, diastolic dysfunction in subjects with diabetes mellitus, edema, essential hypertension, eventual pulmonary embolism, fatty liver disease, heart disease, heart failure, homozygous familial hypercholesterolemia (HoFH), homozygous familial sitosterolemia, hypercholesterolemia, hyperlipidemia, hypertension, hypertriglyceridemia, metabolic syndrome, mixed dyslipidemia, moderate to mild heart failure, myocardial infarction, obesity management, paroxysmal atrial/arterial fibrillation/fibrulation/flutter, paroxysmal supraventricular tachycardias (PSVT), particularly severe or rapid onset edema, platelet aggregation, primary hypercholesterolemia, primary hyperlipidemia, pulmonary arterial hypertension, pulmonary hypertension, recurrent hemodynamically unstable ventricular tachycardia (VT), recurrent ventricular arrhythmias, recurrent ventricular fibrillation (VF), ruptured aneurysm, sitisterolemia, stroke, supraventricular tachycardia, symptomatic atrial fibrillation/flutter, tachycardia, type-II diabetes, vascular disease, venous thromboembolism, and ventricular arrhythmias.

[0028] In one example, there is disclosed a pharmaceutical composition comprising DGLA. In one example, the composition is encapsulated in a capsule shell. In one example, there is disclosed a pharmaceutical composition comprising DGLA encapsulated in a capsule shell comprising gelatin, d-sorbitol and 1,4-sorbitan sugar alcohols. In one example, about 500 mg to about 1 g of DGLA or a derivative thereof is encapsulated in the capsule shell.

[0029] In one example, there is disclosed a method of treating a skin disease or disorder in a subject in need thereof, the method comprising orally administering to the subject a pharmaceutical composition comprising DGLA. Optionally, the pharmaceutical composition comprises DGLA encapsulated in a capsule shell comprising gelatin, d-sorbitol and 1,4-sorbitan sugar alcohols. Optionally, the composition is administered to the subject in an amount sufficient to provide about 1 g to about 4 g of DGLA per day. In one example, the gelatin has a gel mass viscosity of about 9500 to about 11000, for example about 9775 or about 10,500. In another example, the gelatin has a bloom of about 165 to about 190, for example about 170 to about 185. In another example, the gelatin has an ash percentage > than about 0.33.

[0030] In one example, there is disclosed a method of treating overactive bladder in a subject in need thereof, the method comprising orally administering to the subject a pharmaceutical composition comprising DGLA. Optionally, the pharmaceutical composition comprises DGLA encapsulated in a capsule shell comprising gelatin, d-sorbitol and 1,4-sorbitan sugar alcohols. Optionally, the composition is administered to the subject in an amount sufficient to provide about 1 g to about 4 g of DGLA per day. In one example, the gelatin has a gel mass viscosity of about 9500 to about 11000, for example about 9775 or about 10,500. In another example, the gelatin has a bloom of about 165 to about 190, for example about 170 to about 185. In another example, the gelatin has an ash percentage > than about 0.33. These and other embodiments of the invention are described in further detail below.

DETAILED DESCRIPTION

[0031] While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner.

CLAIMS

We claim:

1. A pharmaceutical composition comprising dihomo gamma linolenic acid (DGLA) or a derivative thereof encapsulated in a capsule shell, wherein the composition comprises at least about 80% DGLA by weight of total fatty acids and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid.

2. A pharmaceutical composition comprising dihomo gamma linolenic acid (DGLA) or a derivative thereof encapsulated in a capsule shell comprising gelatin and glycerol , wherein the composition comprises at least about 80% DGLA by weight of total fatty acids and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid.

3. The pharmaceutical composition of claim 1 wherein up to about 1 g of DGLA or a derivative thereof is encapsulated in the capsule shell.

4. The pharmaceutical composition of claim 1 wherein about 200 mg to about 1 g of DGLA or a derivative thereof is encapsulated in the capsule shell.

5. The pharmaceutical composition of claim 1 wherein the gelatin comprises lime bone gelatin and the capsule shell further comprises one or more of: glycerol, purified water, titanium dioxide, medium chain triglycerides and/or lecithin.

6. Use of a pharmaceutical composition comprising dihomo gamma linolenic acid (DGLA) or a derivative thereof in the manufacture of a medicament for treating a skin disease or disorder, wherein the composition comprises at least about 80% DGLA by weight of total fatty acids and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid.

7. The use of claim 6 where the pharmaceutical composition comprises DGLA or a derivative thereof encapsulated in a capsule shell.

8. The use of claim 7 wherein the composition is formulated to provide about 0.2 g to about 8 g of DGLA per day.

9. The use of claim 6 wherein the composition is formulated to be administered in 1 to 8 capsules per day to the subject.

10. The use of claim 9 wherein each capsule comprises about 200 mg to about 1 g of DGLA.

11. Use of a pharmaceutical composition comprising dihomo gamma linolenic acid (DGLA) or a derivative thereof encapsulated in a capsule shell comprising gelatin, d-sorbitol and 1,4-sorbitan sugar alcohols in the manufacture of a medicament for increasing skin DGLA levels or treating a skin disease, wherein the composition comprises at least about 80% DGLA by weight of total fatty acids and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid.

12. A pharmaceutical composition comprising 200 mg to about 1 g of a composition encapsulated in a capsule shell, wherein the composition comprises not less than 95% by weight dihomo gamma linolenic acid (DGLA), not more than 5% of any individual fatty acid selected from 20:2ω6, 20:3ω3, 20:4ω6, 20:4ω3 and 20:5ω3, and not more than 2% by weight unidentified related substances, wherein the composition comprises at least about 80% DGLA by weight of total fatty acids and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid.

13. Use of a pharmaceutical composition comprising at least about 80% dihomo gamma linolenic acid (DGLA) or a derivative thereof by weight of total fatty acids in the composition, and at least one other fatty acid selected from the group consisting of eicosatetraenoic acid, oleic acid, linoleic acid, and eicosadienoic acid, in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof, wherein the disease or disorder is selected from: skin disorders and diseases, including acne vulgaris, acne rosacea, atopic dermatitis, psoriasis, pruritus/itch, radiation protection, dry skin, smooth skin, healthy skin, anti-aging, and photoprotection; urinary disorders and diseases including bladder cancer, cystocele, hematuria, interstitial cystitis, neurogenic bladder, Peyronie's disease, prostate disease, incontinence, urinary tract infection and vasicoureteral reflux; renal disease and disorders including kidney failure, acute kidney injury, chronic kidney disease, and polycystic kidney disease; rheumatic disease including ankylosing spondylitis, fibromyalgia, gout, infectious arthritis, lupus, osteoarthritis, polymyalgia

rheumatic, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, sclerodoma; respiratory disorders including inflammatory lung disease, respiratory tract infections, pleural cavity disease, pulmonary vascular disease, pneumonia, pulmonary embolism, and lung cancer; and cardiovascular disorders including acute cardiac ischemic events, acute myocardial infarction, angina, arrhythmia, atrial fibrulation, atherosclerosis, arterial fibrillation, cardiac insufficiency, cardiovascular disease, chronic heart failure, chronic stable angina, congestive heart failure, coronary artery disease, coronary heart disease, deep vein thrombosis, diabetes, diabetes mellitus, diabetic neuropathy, diastolic dysfunction in subjects with diabetes mellitus, edema, essential hypertension, eventual pulmonary embolism, fatty liver disease, heart disease, heart failure, homozygous familial hypercholesterolemia (HoFH), homozygous familial sitosterolemia, hypercholesterolemia, hyperlipidemia, hypertension, hypertriglyceridemia, metabolic syndrome, mixed dyslipidemia, moderate to mild heart failure, myocardial infarction, obesity management, paroxysmal atrial/arterial fibrillation/fibrulation/flutter, paroxysmal supraventricular tachycardias (PSVT), particularly severe or rapid onset edema, platelet aggregation, primary hypercholesterolemia, primary hyperlipidemia, pulmonary arterial hypertension, pulmonary hypertension, recurrent hemodynamically unstable ventricular tachycardia (VT), recurrent ventricular arrhythmias, recurrent ventricular fibrillation (VF), ruptured aneurysm, sitisterolemia, stroke, supraventricular tachycardia, symptomatic atrial fibrillation/flutter, tachycardia, type-II diabetes, vascular disease, venous thromboembolism, and ventricular arrhythmias.

14. A pharmaceutical composition of any one of claims 1 - 3 for use in treating of skin disorders and diseases, including acne vulgaris, acne rosacea, atopic dermatitis, psoriasis, pruritus/itch, radiation protection, dry skin, smooth skin, healthy skin, anti-aging, and photoprotection; urinary disorders and diseases including bladder cancer, cystocele, hematuria, interstitial cystitis, neurogenic bladder, Peyronie's disease, prostate disease, incontinence, urinary tract infection and vasicoureteral reflux; renal disease and disorders including kidney failure, acute kidney injury, chronic kidney disease, and polycystic kidney disease; rheumatic disease including ankylosing spondylitis, fibromyalgia, gout, infectious arthritis, lupus, osteoarthritis, polymyalgia rheumatic, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, sclerodoma; respiratory disorders including inflammatory lung disease, respiratory tract infections, pleural cavity disease, pulmonary vascular disease, pneumonia, pulmonary embolism, and lung cancer; and cardiovascular disorders including acute cardiac

ischemic events, acute myocardial infarction, angina, arrhythmia, atrial fibrulation, atherosclerosis, arterial fibrillation, cardiac insufficiency, cardiovascular disease, chronic heart failure, chronic stable angina, congestive heart failure, coronary artery disease, coronary heart disease, deep vein thrombosis, diabetes, diabetes mellitus, diabetic neuropathy, diastolic dysfunction in subjects with diabetes mellitus, edema, essential hypertension, eventual pulmonary embolism, fatty liver disease, heart disease, heart failure, homozygous familial hypercholesterolemia (HoFH), homozygous familial sitosterolemia, hypercholesterolemia, hyperlipidemia, hypertension, hypertriglyceridemia, metabolic syndrome, mixed dyslipidemia, moderate to mild heart failure, myocardial infarction, obesity management, paroxysmal atrial/arterial fibrillation/fibrulation/flutter, paroxysmal supraventricular tachycardias (PSVT), particularly severe or rapid onset edema, platelet aggregation, primary hypercholesterolemia, primary hyperlipidemia, pulmonary arterial hypertension, pulmonary hypertension, recurrent hemodynamically unstable ventricular tachycardia (VT), recurrent ventricular arrhythmias, recurrent ventricular fibrillation (VF), ruptured aneurysm, sitisterolemia, stroke, supraventricular tachycardia, symptomatic atrial fibrillation/flutter, tachycardia, type-II diabetes, vascular disease, venous thromboembolism, and ventricular arrhythmias.