discharges without reducing hyperexcited synaptic responses (Hochman et al. *Science* 270:99-102, 1995).

[0006] The cation-chloride co-transporters (CCCs) are important regulators of neuronal chloride concentration that are believed to influence cell-to-cell communication, and various aspects of neuronal development, plasticity, and trauma. The CCC gene family consists of three broad groups: Na^+-$C1^-$ co-transporters (NCCs), K^+-$C1^-$ co-transporters (KCCs) and Na^+-K^+-$2C1^-$ co-transporters (NKCCs). Na-K-Cl co-transport in all cell and tissues is inhibited by loop diuretics, including furosemide, bumetanide, and benzmetanide. Espinosa et al. and Ahmad et al. have previously suggested that furosemide might be useful in the treatment of certain types of epilepsy *(Medicina Espanola* 61:280-281, 1969; and *Brit. J. Clin. Pharmacol.* 3:621-625, 1976). Bumetanide is potentially a more potent drug for treating epilepsy, but it also has a more pronounced diuretic effect. There is therefore a continuing need for methods and compositions for treating neuronal disorders that are not diuretic and that disrupt hypersynchronized neuronal activity without diminishing the neuronal excitability and spontaneous synchronization required for normal functioning of the peripheral and central nervous systems.

SUMMARY

[0006a] In an aspect, there is provided a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers.

[0006b] In another aspect, there is provided the use of a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers in the manufacture of a medicament for treating a patient in need thereof.

[0006c] In another aspect, there is provided a pharmaceutical compositon comprising Bumetanide Dibenzylamide in an oral lymphatic targeted formulation.

[0006d] In another aspect, there is provided a use of a compound or composition as defined above in the manufacture of a medicament for the treatment of epilepsy.

[0006e] In another aspect, there is provided a use of a compound or composition as defined above in the manufacture of a medicament for the treatment of a seizure disorder.

[0006f] In another aspect, there is provided the use of a compound or composition as defined above in the manufacture of a medicament for the treatment of Alzheimer's Disease.

[0007] One example of the present disclosure includes a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers.

[0008] In one example, the composition comprises about 2.5 mg/mL to about 42 mg/mL of Bumetanide Dibenzylamide. In one example, the composition comprises about 0.25%w/w to about 15%w/w of Bumetanide Dibenzylamide. In one example, the composition comprises about 0.1%w/w to about 99.75%w/w of one or more solubilizers. In one example, the one or more solubilizers comprise short chain triglycerides, long chain triglycerides, or combinations thereof. In one example, the one or more solubilizers comprise Polyoxyl 35 Castor Oil, Glyceryl Monolinoleate, or any combination thereof. In one example, the one or more solubilizers comprise Caprylocaproyl Polyoxylglycerides, Phosphatidylcholine, Caprylic/Capric Triglyceride, Lauroyl Plyoxyl-32 Glycerides, Sorbitan Ester, or any combination thereof. In one example, the one or more solubilizers comprise Ethanol,

Propylene Glycol, Polyethylene Glycol 600, Polyethylene Glycol 3350, Oleyl Alcohol, or any combination thereof. In one example, the one or more solubilizers comprise PEG-400, Vitamin E TPGS, or any combination thereof. In one example, the one or more solubilizers comprises soybean oil. In one example, the one or more solubilizers comprises water. In one example, the one or more solubilizers comprise Polyvinylpyrrolidone (K30), Poloxamer 407 (P407), Sodium Carboxymethyl cellulose (CMC), or any combination thereof. In one example, the one or more solubilizers comprises atleast one super disintegrant. In one example, the one or more solubilizers comprises at least one wetting agents. In one example, the one or more solubilizers comprises atleast one surfactants. In one example, the one or more solubilizers comprise Ceolus KG (microcrystalline cellulose), Mannogem EZ (spray dried mannitol), Polyplasdone XL (super disintegrate), Poloxamer 407, Lauroyl Plyoxyl-32 Glycerides, Sorbitan Ester, Neusilin US2 (magnesium aluminometasilicate), Citric acid Monohydrate, Cabosil M5P (fumed silica), Magnesium Stearate, or any combination thereof.

[0009] One example of the present disclosure includes a pharmaceutical composition comprising about 1.79 %w/w of Bumetanide Dibenzylamide, about 33.48 %w/w of Polyoxyl 35 Castor oil, about 32.37 %w/w of Glyceryl Monolinoleate, and about 32.37 %w/w of Soybean oil.

[0010] One example of the present disclosure includes a pharmaceutical composition comprising about 1.76 %w/w of Bumetanide Dibenzylamide, about 32.93 %w/w of Polyoxyl 35 Castor oil, about 31.83 %w/w of Glyceryl Monolinoleate, about 31.83 %w/w of Soybean oil, and about 10.37 %w/w of Ethanol.

[0011] One example of the present disclosure includes a pharmaceutical composition comprising about 1.59 %w/w of Bumetanide Dibenzylamide, about 22 %w/w of Phosphatidylcholine, about 70 %w/w of Caprylocaproyl Polyoxylglycerides, and about 6.41 %w/w of Caprylic/Capric Triglyceride.

[0012] One example of the present disclosure includes a pharmaceutical composition comprising about 1.98 %w/w of Bumetanide Dibenzylamide, about 19.39 %w/w of Lauroyl

Plyoxyl-32 Glycerides, about 37.62 %w/w of Sorbitan Ester, and about 41.01 %w/w of Soybean oil.

[0013] One example of the present disclosure includes a pharmaceutical composition comprising about 1.98 %w/w of Bumetanide Dibenzylamide, about 39.72 %w/w of Caprylocaproyl Polyoxylglycerides, about 25.94 %w/w of Sorbitan Ester, and about 49.78 %w/w of Soybean oil.

[0014] One example of the present disclosure includes a pharmaceutical composition comprising about 1.73 %w/w of Bumetanide Dibenzylamide, about 32.40 %w/w of Polyoxyl 35 Castor oil, about 31.32 %w/w of Glyceryl Monolinoleate, about 31.32 %w/w of Soybean oil, and about 3.24 %w/w of Ethanol.

[0015] One example of the present disclosure includes a pharmaceutical composition comprising about 1.7 %w/w of Bumetanide Dibenzylamide, about 31.91 %w/w of Polyoxyl 35 Castor oil, about 30.85 %w/w of Glyceryl Monolinoleate, about 30.85 %w/w of Soybean oil, and about 4.68 %w/w of Ethanol.

[0016] One example of the present disclosure includes a pharmaceutical composition comprising about 10 %w/w to about 100 %w/w of Caprylocaproyl Polyoxylglycerides. One example of the present disclosure includes a pharmaceutical composition comprising about 12 %w/w to about 20 %w/w of Propylene Glycol. One example of the present disclosure includes a pharmaceutical composition comprising about 57 %w/w to about 80 %w/w of PEG 400. One example of the present disclosure includes a pharmaceutical composition comprising about 1% Vitamin E TPGS.

[0017] One example of the present disclosure includes a pharmaceutical composition comprising about 2.73 %w/w of Bumetanide Dibenzylamide, about 10 % w/w of Caprylocaproyl Polyoxylglycerides, about 12.05 %w/w of Propylene Glycol, about 67.22 %w/w of Polyethylene Glycol 400, and about 8 %w/w of Water.

[0018] One example of the present disclosure includes a pharmaceutical composition comprising about 2.82 %w/w of Bumetanide Dibenzylamide, about 4.65 % w/w of

Caprylocaproyl Polyoxylglycerides, about 13.01 %w/w of Propylene Glycol, about 67.97 %w/w of Polyethylene Glycol 400, about 0.92 %w/w Polyvinylpyrrolidone (K30), and about 10.62 %w/w of Water.

[0019] One example of the present disclosure includes a pharmaceutical composition comprising about 0.6 %w/w of Bumetanide Dibenzylamide, about 10 %w/w of Caprylocaproyl Polyoxylglycerides, about 9.15 %w/w of Propylene Glycol, about 53.84 %w/w of Polyethylene Glycol 400, about 3.6 %w/w of Polyvinylpyrrolidone (K30), about 2.4 %w/w of Poloxamer 407 (P407), about 0.41 %w/w Sodium CMC, and about 20 %w/w of water.

[0020] One example of the present disclosure includes a pharmaceutical composition comprising about 0.6 %w/w of Bumetanide Dibenzylamide, about 10 %w/w of Caprylocaproyl Polyoxylglycerides, about 9.15 %w/w of Propylene Glycol, about 66.75 %w/w of Polyethylene Glycol 400, about 3. %w/w of Polyvinylpyrrolidone (K30), about 2.4 %w/w of Poloxamer 407 (P407), and about 7.5 %w/w of Polyethylene Glycol 3350.

[0021] One example of the present disclosure includes a pharmaceutical composition comprising about 15 %w of Bumetanide Dibenzylamide, about 20 %w of Microcrystalline Cellulose, about 51 %w of Spray Dried Mannitol, about 7 %w of Polyplasdone XL (super disintegrant), about 3% w of Poloxamer 407, about 1.5 %w of Citric Acid Monohydrate, about 1.0 %w of Cabosil M5P (fumed silica), and about 1.5 %w of Magnesium Stearate.

[0022] One example of the present disclosure includes a pharmaceutical composition comprising about 7.4 %w of Bumetanide Dibenzylamide, about 9.9 %w of Lauroyl Plyoxyl-32 Glycerides, about 9.9 %w of Sorbitan Ester, about 54.3 %w of Polyplasdone XL (super disintegrate), about 0.5% w of Poloxamer 407, about 0.7 %w of Citric Acid Monohydrate, about 2.0 %w of Cabosil M5P (fumed silica), about 14.8 %w of Neusilin US2 (magnesium aluminometasilicate), and about 0.5 %w of Magnesium Stearate.

[0023] One example of the present disclosure includes a pharmaceutical composition comprising a vehicle composition comprising 55 % Polyethylene Glycol 400 (PEG-400) in water, or 41 % PEG-400, 12 % Ethanol, 47 % water or 45 % PEG-400, 10 % DMSO, 45 %

water, or 31 % PEG-400, 31 % Tetraglycol, 15 % Caprylocaproyl Polyoxylglycerides, 23 % water, or 30 % PEG-400, 10 % N-Methyl Pyrrolidone, 10 % DMSO, 50 % water, or 25 % PEG-400, 10 % DMSO, 20 % Tetraglycol, 45 % water, or 20 % Ethanol in water, or 20% Hydroxypropyl-β-Cyclodextrin in water, or 11% DMSO, 22% PEG-400, 22% Tetraglycol, 44% water, or 44% PEG-400, 0.4% Poloxamer-188, 22% N-Methyl Pyrrolidone, 33% water, or 20% PEG-400, 15% Hydroxypropyl-β-Cyclodextrin in water, or 40% PEG-400, 20% Propylene Glycol, 5% Ethanol and 35%, water.

[0024] One example of the present disclosure includes a pharmaceutical composition comprising about 28 g of Bumetanide Dibenzylamide, and about 3 ml of a solvent, wherein 50 g of solvent comprises about 5g of Caprylocaproyl Polyoxylglycerides, about 10g of Propylene Glycol, about 28.5g of PEG-400, about 0.5g of Vitamin E TPGS, about 1g of Ethanol, and about 4.5g of water.

[0025] One example of the present disclosure includes a method for treating a patient in need thereof comprising: administering a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers.

[0026] In an alternative example, the present disclosure includes a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers for use in mecidine.

[0027] In a further alternative example, there is provided use of a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers in the manufacture of a medicament. In a further example, a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers may used of the manufacture of a medicament for the therapeutic and/or prophylactic treatment of seizure, epilepsy, and/or other indications such as neuropathic pain. In some examples, a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers may used of the manufacture of a medicament for the therapeutic and/or prophylactic treatment of epilepsy and/or neurological syndromes that are specific to children. In some examples, a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers may used of the manufacture of a medicament for

the therapeutic and/or prophylactic treatment of one or more indications listed in Figure 18 (Fisher et al.) and for treating whatever terms might replace the old and current terms describing the indications listed in Figure 18 in the future. In some examples, a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers may used of the manufacture of a medicament for the therapeutic and/or prophylactic treatment of migraines or tinnitus. In some examples, a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers may used of the manufacture of a medicament for the therapeutic and/or prophylactic treatment of depression and/or anxiety. In some examples, a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers may used of the manufacture of a medicament for the therapeutic and/or prophylactic treatment of psychoneurotic disorders. In some examples, a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers may used of the manufacture of a medicament for the therapeutic and/or prophylactic treatment of neurodegenerative disorders including but not limited to Alzheimer's disease, amyotropihc lateral sclerosis, Friedrich ataxia, Huntington's Disease, Lewy Body disease, Parkinson's disease, or spinal muscular atrophy.In one example, the pharmaceutical composition comprises about 2.5 mg/mL to about 42 mg/mL of Bumetanide Dibenzylamide. In one example, the pharmaceutical composition comprises about 0.25%w/w to about 15%w/w of Bumetanide Dibenzylamide. In one example, the one or more solubilizers comprise short chain triglycerides, long chain triglycerides, or combinations thereof. In one example, the one or more solubilizers comprise polyoxyl 35 castor oil, Glyceryl Monolinoleate, or any combination thereof. In one example, the one or more solubilizers comprise Caprylocaproyl Polyoxylglycerides, Phosphatidylcholine, Caprylic/Capric Triglyceride, Lauroyl Plyoxyl-32 Glycerides, Sorbitan Ester or any combination thereof. In one example, the one or more solubilizers comprise Ethanol, Propylene Glycol, Polyethylene Glycol 600, Polyethylene Glycol 3350, Oleyl Alcohol, or any combination thereof. In one example, the one or more solubilizers comprise PEG-400, Vitamin E TPGS, or any combination thereof. In one example, the one or more solubilizers comprises Soybean oil. In one example, the one or more solubilizers comprises water. In one example, the one or more solubilizers comprise Polyvinylpyrrolidone (K30), Poloxamer 407 (P407), Sodium Carboxymethyl cellulose (CMC), or any combination thereof. In one

example, the one or more solubilizers comprises at least one super disintegrant. In one example, the one or more solubilizers comprises at least one wetting agent. In one example, the one or more solubilizers comprises atleast one surfactant. In one example, the one or more solubilizers comprise Ceolus KG (microcrystalline cellulose), Mannogem EZ (spray dried mannitol), Polyplasdone XL (super disintegrate), Poloxamer 407, lauroyl plyoxyl-32 glycerides, sorbitan ester, Neusilin US2 (magnesium aluminometasilicate), Citric acid Monohydrate, Cabosil M5P (fumed silica), Magnesium Stearate or any combination thereof. In one example, the pharmaceutical composition comprising about 1.79 %w/w of Bumetanide Dibenzylamide, about 33.48 %w/w of Polyoxyl 35 Castor oil, about 32.37 %w/w of Glyceryl Monolinoleate, and about 32.37 %w/w of Soybean oil. In one example, the pharmaceutical composition comprising about 1.76 %w/w of Bumetanide Dibenzylamide, about 32.93 %w/w of Polyoxyl 35 Castor oil, about 31.83 %w/w of Glyceryl Monolinoleate, about 31.83 %w/w of Soybean oil, and about 10.37 %w/w of Ethanol. In one example, the pharmaceutical composition comprising about 1.59 %w/w of Bumetanide Dibenzylamide, about 22 %w/w of Phosphatidylcholine, about 70 %w/w of Caprylocaproyl Polyoxylglycerides, and about 6.41 %w/w of Caprylic/Capric Triglyceride. In one example, the pharmaceutical composition comprising about 1.98 %w/w of Bumetanide Dibenzylamide, about 19.39 %w/w of Lauroyl Plyoxyl-32 Glycerides, about 37.62 %w/w of Sorbitan Ester, and about 41.01 %w/w of Soybean oil. In one example, the pharmaceutical composition comprising about 1.98 %w/w of Bumetanide Dibenzylamide, about 39.72 %w/w of Caprylocaproyl Polyoxylglycerides, about 25.94 %w/w of Sorbitan Ester, and about 49.78 %w/w of Soybean oil. In one example, the pharmaceutical composition comprising about 1.73 %w/w of Bumetanide Dibenzylamide, about 32.40 %w/w of Polyoxyl 35 Castor oil, about 31.32 %w/w of Glyceryl Monolinoleate, about 31.32 %w/w of Soybean oil, and about 3.24 %w/w of Ethanol. In one example, the pharmaceutical composition comprising about 1.7 %w/w of Bumetanide Dibenzylamide, about 31.91 %w/w of Polyoxyl 35 Castor oil, about 30.85 %w/w of Glyceryl Monolinoleate, about 30.85 %w/w of Soybean oil, and about 4.68 %w/w of Ethanol. In one example, the pharmaceutical composition comprising about 10 %w/w to about 100 %w/w of Caprylocaproyl Polyoxylglycerides. In one example, the pharmaceutical composition comprising about 12 %w/w to about 20 %w/w of Propylene Glycol. In one example, the pharmaceutical

composition comprising about 57 %w/w to about 80 %w/w of PEG 400. In one example, the pharmaceutical composition comprising about 1% Vitamin E TPGS. In one example, the pharmaceutical composition comprising about 2.73 %w/w of Bumetanide Dibenzylamide, about 10 % w/w of Caprylocaproyl Polyoxylglycerides, about 12.05 %w/w of Propylene Glycol, about 67.22 %w/w of Polyethylene Glycol 400, and about 8 %w/w of Water. In one example, the pharmaceutical composition comprising about 2.82 %w/w of Bumetanide Dibenzylamide, about 4.65 % w/w of Caprylocaproyl Polyoxylglycerides, about 13.01 %w/w of Propylene Glycol, about 67.97 %w/w of Polyethylene Glycol 400, about 0.92 %w/w Polyvinylpyrrolidone (K30), and about 10.62 %w/w of Water. In one example, the pharmaceutical composition comprising about 0.6 %w/w of Bumetanide Dibenzylamide, about 10 %w/w of Caprylocaproyl Polyoxylglycerides, about 9.15 %w/w of Propylene Glycol, about 53.84 %w/w of Polyethylene Glycol 400, about 3.6 %w/w of Polyvinylpyrrolidone (K30), about 2.4 %w/w of Poloxamer 407 (P407), about 0.41 %w/w Sodium CMC, and about 20 %w/w of water. In one example, the pharmaceutical composition comprising about 0.6 %w/w of Bumetanide Dibenzylamide, about 10 %w/w of Caprylocaproyl Polyoxylglycerides, about 9.15 %w/w of Propylene Glycol, about 66.75 %w/w of Polyethylene Glycol 400, about 3.6 %w/w of Polyvinylpyrrolidone (K30), about 2.4 %w/w of Poloxamer 407 (P407), and about 7.5 %w/w of Polyethylene Glycol 3350. In one example, the pharmaceutical composition comprising about 15 %w of Bumetanide Dibenzylamide, about 20 %w of Microcrystalline Cellulose, about 51 %w of Spray Dried Mannitol, about 7 %w of Polyplasdone XL (super disintegrate), about 3% w of Poloxamer 407, about 1.5 %w of Citric Acid Monohydrate, about 1.0 %w of Cabosil M5P (fumed silica), and about 1.5 %w of Magnesium Stearate. In one example, the pharmaceutical composition comprising about 7.4 %w of Bumetanide Dibenzylamide, about 9.9 %w of Lauroyl Plyoxyl-32 Glycerides, about 9.9 %w of Sorbitan Ester, about 54.3 %w of Polyplasdone XL (super disintegrate), about 0.5% w of Poloxamer 407, about 0.7 %w of Citric Acid Monohydrate, about 2.0 %w of Cabosil M5P (fumed silica), about 14.8 %w of Neusilin US2 (magnesium aluminometasilicate), and about 0.5 %w of Magnesium Stearate. In one example, the pharmaceutical composition comprising a vehicle composition comprising 55 Polyethylene Glycol 400 (PEG-400) in water, or 41 % PEG-400, 12 % ethanol, 47 % water or 45 % PEG-400, 10 % DMSO, 45 % water, or 31 % PEG-400, 31 % Tetraglycol, 15 %

Caprylocaproyl Polyoxylglycerides, 23 % water, or 30 % PEG-400, 10 % N-Methyl Pyrrolidone, 10 % DMSO, 50 % water, or 25 % PEG-400, 10 % DMSO, 20 % Tetraglycol, 45 % water, or 20 % Ethanol in water, or 20% Hydroxypropyl-β-Cyclodextrin in water, or 11% DMSO, 22% PEG-400, 22% Tetraglycol, 44 % water, or 44 % PEG-400, 0.4 % Poloxamer-188, 22 % N-Methyl pyrrolidone, 33 % water, or 20 % PEG-400, 15 % Hydroxypropyl-β-Cyclodextrin in water, or 40 % PEG-400, 20 % Propylene Glycol, 5% Ethanol, and 35% water. In one example, the pharmaceutical composition comprising about 28 g of Bumetanide Dibenzylamide, and about 3 ml of a solvent, wherein 50 g of solvent comprises about 5g of Caprylocaproyl Polyoxylglycerides, about 10g of Propylene Glycol, about 28.5g of PEG-400, about 0.5g of Vitamin E TPGS, about 1g of Ethanol, and about 4.5g of water. In one example, the pharmaceutical composition is an oral capsule. In one example, the pharmaceutical composition is a nasal solution. In one example, the pharmaceutical composition is a rectal gel. In one example, the pharmaceutical composition is a rectal paste. In one example, the pharmaceutical composition is a sublingual tablet. In one example, the pharmaceutical composition is an injectable composition. In one example, the dosing of the patient with the pharmaceutical composition is done orally. In one example, the dosing of the patient with the pharmaceutical composition is done intranasally. In one example, the dosing of the patient with the pharmaceutical composition is done rectally. In one example, the dosing of the patient with the pharmaceutical composition is done sublingually. In one example, the dosing of the patient with the pharmaceutical composition is done subcutaneously. In one example, the dosing of the patient with the pharmaceutical composition is done intramuscularly.

[0028] One example of the present disclosure includes a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more organic anion transport (OAT) inhibitors. The role of active transport in tissue distribution of bumetanide has been extensively studied for the kidney and the liver but not the BBB. In mice and humans, OATs are thought to mediate the renal transport of bumetanide. These transporters maybe essentially related to the transport of bumetanide on the luminal and basolateral membrane site of the kidney proximal tubular cells. Bumetanide seems not to be transported by OATPs in kidney or liver, although only few members of this transporter family have been studied in this respect. Probenecid inhibits OATs which explains that it has been shown to reduce the plasma and renal clearance of

bumetanide in dogs. In line with these observations in dogs, probenecid markedly increased the plasma half-life of bumetanide in mice. However, it did not decrease the diuretic effect of bumetanide. Systemic administration of an organic anion transport inhibitor may have a beneficial effect on brain levels of bumetanide or products thereof. For background teaching, see Tollner et al., European Journal of Pharmacology, 746 (2015) 167-173, herein incorporated by reference with regard to such teaching.

[0029] In one example, the one or more OAT inhibitors are competitive antagonists. In one example, the Bumetanide Dibenzylamide and the one or more OAT inhibitors are formulated with different release profiles. In one example, the at least one OAT inhibitor is formulated to be released prior to release of the Bumetanide Dibenzylamide. In one example, the at least one OAT inhibitor is formulated to be released prior to the Bumetanide Dibenzylamide achieving maximum plasma concentration (C_{max}) in a patient receiving the composition. In one example, wherein the one or more OAT inhibitor is selected from the group consisting of probenecid, aspirin, ibuprofen, acetylsalicylic acid, diclofenac, aspartame, and valproic acid.

[0030] One example of the present disclosure includes a pharmaceutical composition comprising Bumetanide Dibenzylamide in a self-emulsifying drug delivery system (SEDDS). In one example, the SEDDS comprises an isotropic mixture of oils, solubilizers, surfactants, and co-solvents.

[0031] One example of the present disclosure includes a pharmaceutical composition comprising Bumetanide Dibenzylamide in an oral lymphatic targeted formulation.

[0032] In one example, the composition comprises Bumetanide Dibenzylamide, Polyoxyl 35 Castor Oil (Kolliphor EL), Glyceryl Monolinoleate (Maisine CC), Soybean Oil, and Ethanol. In one example, the composition comprises about 1 to 2 w/w% Bumetanide Dibenzylamide, about 30 to 35 w/w% Polyoxyl 35 Castor Oil (Kolliphor EL), about 30 to 35 w/w% Glyceryl Monolinoleate (Maisine CC), about 30 to 35 w/w% Soybean Oil, and about 2.5 to 5 w/w% Ethanol. In one example, the composition comprises about 1.7 w/w% Bumetanide Dibenzylamide, about 32.4 w/w% Polyoxyl 35 Castor Oil (Kolliphor EL), about 31.3 w/w% Glyceryl Monolinoleate (Maisine CC), about 31.3 w/w% Soybean Oil, and about 3.2 w/w% Ethanol.

[0033] One example of the present disclosure includes a pharmaceutical composition comprising a prodrug of Bumetanide and one or more oral lymphatic targeting excipients. A prodrug of Bumetanide may include any compound comprising Bumetanide including but not limited to amide prodrug forms, which have been demonstrated to offer one or more unexpected benefits over other prodrug forms.

[0034] In one example, the prodrug of Bumetanide is an amide prodrug. In one example, the prodrug of Bumetanide is one or more of Bumetanide Dibenzylamide, Bumetanide Diethylamide, and Bumetanide Morpholinoamide. In one example the composition comprises alkoxylated castor oil. In one example the composition comprises Polyoxyl 35 Castor Oil (Kolliphor EL). In one example the composition comprises one or more of a mono-, di-, and triglyceride. In one example the composition comprises Glyceryl Monolinoleate (Maisine CC). In one example the composition comprises a fixed oil. In one example, the compositon comprises soybean oil. In one example the composition comprises a water soluble solvent. In one example, the compositon comprises ethanol.

[0035] For the avoidance of doubt, the prodrugs of Bumetanide described herein (e.g. Bumetanide Dibenzylamide, Bumetanide Diethylamide, and Bumetanide Morpholinoamide), and compositions comprising prodrugs of Bumetanide, may be suitable and/or preferred treatment agents for use in the methods of the present disclosure (including all examples of those methods). The prodrugs of Bumetanide may be used to treat epilepsy, Alzheimer, and other diseases and indication comprsising seizure.

[0036] In one example, the pharmaceutical composition comprises up to 17.5 %w of Bumetanide Dibenzylamide, about 20 %w solublizer, and about 15 %w absorbant.

[0037] Throughout the present disclosure, any description of a method may be interpreted to describe and support a commensurate use, manufacture for use, composition, composition for use, or other alternative description.

[0038] One or more examples may be incorporated in a different example or although not specifically described. That is, all examples can be combined in any way or combination.

CLAIMS

That which is claimed is:

1. A pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers.

2. The composition of claim 1, wherein the composition comprises about 2.5 mg/mL to about 42 mg/mL of Bumetanide Dibenzylamide.

3. The composition of claim 1 or 2, wherein the composition comprises about 0.25%w/w to about 15%w/w of Bumetanide Dibenzylamide.

4. The composition of claim 1-3, wherein the composition comprises about 0.1%w/w to about 99.75%w/w of one or more solubilizers.

5. The composition of any one of claims 1–4, wherein the one or more solubilizers are selected from the group consisting of short chain triglycerides, long chain triglycerides, and combinations thereof.

6. The composition of any one of claims 1–5, wherein the one or more solubilizers are selected from the group consisting of Polyoxyl 35 Castor Oil, Glyceryl Monolinoleate, and any combination thereof.

7. The composition of any one of claims 1–6, wherein the one or more solubilizers are selected from the group consisting of Caprylocaproyl Polyoxylglycerides, Phosphatidylcholine, Caprylic/Capric Triglyceride, Lauroyl Plyoxyl-32 Glycerides, Sorbitan Ester, and any combination thereof.

8. The composition of any one of claims 1–7, wherein the one or more solubilizers are selected from the group consisting of Ethanol, Propylene Glycol, Polyethylene Glycol 600, Polyethylene Glycol 3350, Oleyl Alcohol, and any combination thereof.

9. The composition of any one of claims 1–7, wherein the one or more solubilizers are selected from the group consisting of PEG-400, Vitamin E TPGS, and any combination thereof.

10. The composition of any one of claims 1–9, wherein at least one of the one or more solubilizers is soybean oil.

11 The composition of any one of claims 1–10, wherein the composition comprises water.

12. The composition of any one of claims 1–11, wherein the one or more solubilizers are selected from the group consisting of Polyvinylpyrrolidone (K30), Poloxamer 407 (P407), Sodium Carboxymethyl cellulose (CMC), and any combination thereof.

13. The composition of any one of claims 1-12, further comprising at least one super disintegrant.

14. The composition of any one of claims 1-13, further comprising at least one wetting agent.

15. The composition of any one of claims 1-14, further comprising at least one surfactant.

16. The composition of any one of claims 1–15, wherein the composition comprises Ceolus KG (microcrystalline cellulose), Mannogem EZ (spray dried mannitol), Polyplasdone XL (super disintegrant), Poloxamer 407, Lauroyl Polyoxyl-32 Glycerides, Sorbitan Ester, Neusilin US2 (magnesium aluminometasilicate), Citric acid Monohydrate, Cabosil M5P (fumed silica), Magnesium Stearate, or any sub-combination thereof.

17. A pharmaceutical composition of any one of claims 1-16, comprising about 1.79 %w/w of Bumetanide Dibenzylamide, about 33.48 %w/w of Polyoxyl 35 Castor oil, about 32.37 %w/w of Glyceryl Monolinoleate, and about 32.37 %w/w of Soybean oil.

18. A pharmaceutical composition of any one of claims 1-16, comprising about 1.76 %w/w of Bumetanide Dibenzylamide, about 32.93 %w/w of Polyoxyl 35 Castor oil, about 31.83 %w/w of Glyceryl Monolinoleate, about 31.83 %w/w of Soybean oil, and about 10.37 %w/w of Ethanol.

19. A pharmaceutical composition of any one of claims 1-16, comprising about 1.59 %w/w of Bumetanide Dibenzylamide, about 22 %w/w of Phosphatidylcholine, about 70 %w/w of Caprylocaproyl Polyoxylglycerides, and about 6.41 %w/w of Caprylic/Capric Triglyceride.

20. A pharmaceutical composition of any one of claims 1-16, comprising about 1.98 %w/w of Bumetanide Dibenzylamide, about 19.39 %w/w of Lauroyl Plyoxyl-32 Glycerides, about 37.62 %w/w of Sorbitan Ester, and about 41.01 %w/w of Soybean oil.

21. A pharmaceutical composition of any one of claims 1-16, comprising about 1.98 %w/w of Bumetanide Dibenzylamide, about 39.72 %w/w of Caprylocaproyl Polyoxylglycerides, about 25.94 %w/w of Sorbitan Ester, and about 49.78 %w/w of Soybean oil.

22. A pharmaceutical composition of any one of claims 1-16, comprising about 1.73 %w/w of Bumetanide Dibenzylamide, about 32.40 %w/w of Polyoxyl 35 Castor oil, about 31.32 %w/w of Glyceryl Monolinoleate, about 31.32 %w/w of Soybean oil, and about 3.24 %w/w of Ethanol.

23. A pharmaceutical composition of any one of claims 1-16, comprising about 1.7 %w/w of Bumetanide Dibenzylamide, about 31.91 %w/w of Polyoxyl 35 Castor oil, about 30.85 %w/w of Glyceryl Monolinoleate, about 30.85 %w/w of Soybean oil, and about 4.68 %w/w of Ethanol.

24. The pharmaceutical composition of any one of claims 1 – 23, comprising about 10 %w/w to about 100 %w/w of Caprylocaproyl Polyoxylglycerides.

25. The pharmaceutical composition of any one of claims 1 – 24, comprising about 12 %w/w to about 20 %w/w of Propylene Glycol.

26. The pharmaceutical composition of any one of claims 1 – 25 comprising about 57 %w/w to about 80 %w/w of PEG 400.

27. The pharmaceutical composition of any one of claims 1 – 26 comprising about 1% Vitamin E TPGS.

28. A pharmaceutical composition of any one of the claims 1- 27, comprising about 2.73 %w/w of Bumetanide Dibenzylamide, about 10 % w/w of Caprylocaproyl Polyoxylglycerides, about 12.05 %w/w of Propylene Glycol, about 67.22 %w/w of Polyethylene Glycol 400, and about 8 %w/w of Water.

29. A pharmaceutical composition of any one of the claims 1- 27, comprising about 2.82 %w/w of Bumetanide Dibenzylamide, about 4.65 % w/w of Caprylocaproyl Polyoxylglycerides, about 13.01 %w/w of Propylene Glycol, about 67.97 %w/w of Polyethylene Glycol 400, about 0.92 %w/w Polyvinylpyrrolidone (K30), and about 10.62 %w/w of Water.

30. A pharmaceutical composition of any one of the claims 1- 27, comprising about 0.6 %w/w of Bumetanide Dibenzylamide, about 10 %w/w of Caprylocaproyl Polyoxylglycerides, about 9.15 %w/w of Propylene Glycol, about 53.84 %w/w of Polyethylene Glycol 400, about 3.6 %w/w of Polyvinylpyrrolidone (K30), about 2.4 %w/w of Poloxamer 407 (P407), about 0.41 %w/w Sodium CMC, and about 20 %w/w of water.

31. A pharmaceutical composition of any one of the claims 1- 27, comprising about 0.6 %w/w of Bumetanide Dibenzylamide, about 10 %w/w of Caprylocaproyl Polyoxylglycerides, about 9.15 %w/w of Propylene Glycol, about 66.75 %w/w of Polyethylene Glycol 400, about 3.6 %w/w of Polyvinylpyrrolidone (K30), about 2.4 %w/w of Poloxamer 407 (P407), and about 7.5 %w/w of Polyethylene Glycol 3350.

32. A pharmaceutical composition of any one of the claims 1- 27, comprising about 15 %w of Bumetanide Dibenzylamide, about 20 %w of Microcrystalline Cellulose, about 51 %w of Spray Dried Mannitol, about 7 %w of Polyplasdone XL (super disintegrate), about 3% w of Poloxamer 407, about 1.5 %w of Citric Acid Monohydrate, about 1.0 %w of Cabosil M5P (fumed silica), and about 1.5 %w of Magnesium Stearate.

33. A pharmaceutical composition of any one of the claims 1- 27, comprising about 7.4 %w of Bumetanide Dibenzylamide, about 9.9 %w of Lauroyl Plyoxyl-32 Glycerides, about 9.9 %w of Sorbitan Ester, about 54.3 %w of Polyplasdone XL (super disintegrate), about 0.5% w of Poloxamer 407, about 0.7 %w of Citric Acid Monohydrate, about 2.0 %w of Cabosil M5P (fumed silica), about 14.8 %w of Neusilin US2 (magnesium aluminometasilicate), and about 0.5 %w of Magnesium Stearate.

34. A pharmaceutical composition comprising of any one of the claims 1- 27, a vehicle composition comprising 55 % Polyethylene Glycol 400 (PEG-400) in water, or 41 % PEG-400,

12 % Ethanol, 47 % water or 45 % PEG-400, 10 % DMSO, 45 % water, or 31 % PEG-400, 31 % Tetraglycol, 15 % Caprylocaproyl Polyoxylglycerides, 23 % water, or 30 % PEG-400, 10 % N-Methyl Pyrrolidone, 10 % DMSO, 50 % water, or 25 % PEG-400, 10 % DMSO, 20 % Tetraglycol, 45 % water, or 20 % Ethanol in water, or 20% Hydroxypropyl-β-Cyclodextrin in water, or 11% DMSO, 22% PEG-400, 22% Tetraglycol, 44% water, or 44% PEG-400, 0.4% Poloxamer-188, 22% N-Methyl Pyrrolidone, 33% water, or 20% PEG-400, 15% Hydroxypropyl-β-Cyclodextrin in water, or 40% PEG-400, 20% Propylene Glycol, 5% Ethanol and 35%, water.

35. A pharmaceutical composition of any one of the claims 1- 27, comprising about 28 g of Bumetanide Dibenzylamide, and about 3 ml of a solvent, wherein 50 g of solvent comprises about 5g of Caprylocaproyl Polyoxylglycerides, about 10g of Propylene Glycol, about 28.5g of PEG-400, about 0.5g of Vitamin E TPGS, about 1g of Ethanol, and about 4.5g of water.

36. Use of a pharmaceutical composition comprising Bumetanide Dibenzylamide and one or more solubilizers in the manufacture of a medicament for treating a patient in need thereof.

37. The use of claim 36, wherein the pharmaceutical composition comprises about 2.5 mg/mL to about 42 mg/mL of Bumetanide Dibenzylamide.

38. The use of any one of the claims 36-37, wherein the pharmaceutical composition comprises about 0.25%w/w to about 15%w/w of Bumetanide Dibenzylamide.

39. The use of any one of the claims 36-38, wherein the one or more solubilizers comprise short chain triglycerides, long chain triglycerides, or combinations thereof.

40. The use of any one of the claims 36-39, wherein the composition comprises about 0.1%w/w to about 99.75%w/w of one or more solubilizers

41. The use of any one of the claims 36-40, wherein the one or more solubilizers comprise polyoxyl 35 castor oil, Glyceryl Monolinoleate, or any combination thereof.

42. The use of any one of the claims 36-41, wherein the one or more solubilizers comprise Caprylocaproyl Polyoxylglycerides, Phosphatidylcholine, Caprylic/Capric Triglyceride, Lauroyl Plyoxyl-32 Glycerides, Sorbitan Ester or any combination thereof.

43. The use of any one of the claims 36-42, wherein the one or more solubilizers comprise Ethanol, Propylene Glycol, Polyethylene Glycol 600, Polyethylene Glycol 3350, Oleyl Alcohol, or any combination thereof.

44. The use of any one of the claims 36-43, wherein the one or more solubilizers comprise PEG-400, Vitamin E TPGS, or any combination thereof.

45. The use of any one of the claims 36-44, wherein the one or more solubilizers comprises Soybean oil.

46. The use of any one of the claims 36-45, wherein the one or more solubilizers comprises water.

47. The use of any one of the claims 36-46, wherein the one or more solubilizers comprise Polyvinylpyrrolidone (K30), Poloxamer 407 (P407), Sodium Carboxymethyl cellulose (CMC), or any combination thereof.

48. The use of any one of the claims 36-47, wherein the one or more solubilizers comprises at least one super disintegrant.

49. The use of any one of the claims 36-48, wherein the one or more solubilizers comprises at least one wetting agent.

50. The use of any one of the claim 36-49, wherein the one or more solubilizers comprises at least one surfactant.

51. The use of any one of the claim 36-50, wherein the one or more solubilizers comprises Ceolus KG (microcrystalline cellulose), Mannogem EZ (spray dried mannitol), Polyplasdone XL (super disintegrant), Poloxamer 407, lauroyl plyoxyl-32 glycerides, sorbitan ester, Neusilin US2 (magnesium aluminometasilicate), Citric acid Monohydrate, Cabosil M5P (fumed silica), Magnesium Stearate or any combination thereof.

52. The use of claim 36, wherein the pharmaceutical composition comprises about 1.79 %w/w of Bumetanide Dibenzylamide, about 33.48 %w/w of Polyoxyl 35 Castor oil, about 32.37 %w/w of Glyceryl Monolinoleate, and about 32.37 %w/w of Soybean oil.

53. The use of claim 36, wherein the pharmaceutical composition comprises about 1.76 %w/w of Bumetanide Dibenzylamide, about 32.93 %w/w of Polyoxyl 35 Castor oil, about 31.83 %w/w of Glyceryl Monolinoleate, about 31.83 %w/w of Soybean oil, and about 10.37 %w/w of Ethanol.

54. The use of claim 36, wherein the pharmaceutical composition comprises about 1.59 %w/w of Bumetanide Dibenzylamide, about 22 %w/w of Phosphatidylcholine, about 70 %w/w of Caprylocaproyl Polyoxylglycerides, and about 6.41 %w/w of Caprylic/Capric Triglyceride.

55. The use of claim 36, wherein the pharmaceutical composition comprises about 1.98 %w/w of Bumetanide Dibenzylamide, about 19.39 %w/w of Lauroyl Plyoxyl-32 Glycerides, about 37.62 %w/w of Sorbitan Ester, and about 41.01 %w/w of Soybean oil.

56. The use of claim 36, wherein the pharmaceutical composition comprises about 1.98 %w/w of Bumetanide Dibenzylamide, about 39.72 %w/w of Caprylocaproyl Polyoxylglycerides, about 25.94 %w/w of Sorbitan Ester, and about 49.78 %w/w of Soybean oil.

57. The use of claim 36, wherein the pharmaceutical composition comprises about 1.73 %w/w of Bumetanide Dibenzylamide, about 32.40 %w/w of Polyoxyl 35 Castor oil, about

31.32 %w/w of Glyceryl Monolinoleate, about 31.32 %w/w of Soybean oil, and about 3.24 %w/w of Ethanol.

58. The use of claim 36, wherein the pharmaceutical composition comprises about 1.7 %w/w of Bumetanide Dibenzylamide, about 31.91 %w/w of Polyoxyl 35 Castor oil, about 30.85 %w/w of Glyceryl Monolinoleate, about 30.85 %w/w of Soybean oil, and about 4.68 %w/w of Ethanol.

59. The use of claim 36, wherein the pharmaceutical composition comprises about 10 %w/w to about 100 %w/w of Caprylocaproyl Polyoxylglycerides.

60. The use of claim 36, wherein the pharmaceutical composition comprises about 12 %w/w to about 20 %w/w of Propylene Glycol.

61. The use of claim 36, wherein the pharmaceutical composition comprises about 57 %w/w to about 80 %w/w of PEG 400.

62. The use of claim 36, wherein the pharmaceutical composition comprises about 1% Vitamin E TPGS.

63. The use of claim 36, wherein the pharmaceutical composition comprises about 2.73 %w/w of Bumetanide Dibenzylamide, about 10 % w/w of Caprylocaproyl Polyoxylglycerides, about 12.05 %w/w of Propylene Glycol, about 67.22 %w/w of Polyethylene Glycol 400, and about 8 %w/w of Water.

64. The use of claim 36, wherein the pharmaceutical composition comprises about 2.82 %w/w of Bumetanide Dibenzylamide, about 4.65 % w/w of Caprylocaproyl Polyoxylglycerides, about 13.01 %w/w of Propylene Glycol, about 67.97 %w/w of Polyethylene Glycol 400, about 0.92 %w/w Polyvinylpyrrolidone (K30), and about 10.62 %w/w of Water.

65. The use of claim 36, wherein the pharmaceutical composition comprises about 0.6 %w/w of Bumetanide Dibenzylamide, about 10 %w/w of Caprylocaproyl Polyoxylglycerides, about 9.15 %w/w of Propylene Glycol, about 53.84 %w/w of Polyethylene Glycol 400, about 3.6 %w/w of Polyvinylpyrrolidone (K30), about 2.4 %w/w of Poloxamer 407 (P407), about 0.41 %w/w Sodium CMC, and about 20 %w/w of water.

66. The use of claim 36, wherein the pharmaceutical composition comprises about 0.6 %w/w of Bumetanide Dibenzylamide, about 10 %w/w of Caprylocaproyl Polyoxylglycerides, about 9.15 %w/w of Propylene Glycol, about 66.75 %w/w of Polyethylene Glycol 400, about 3.6 %w/w of Polyvinylpyrrolidone (K30), about 2.4 %w/w of Poloxamer 407 (P407), and about 7.5 %w/w of Polyethylene Glycol 3350.

67. The use of claim 36, wherein the pharmaceutical composition comprises about 15 %w of Bumetanide Dibenzylamide, about 20 %w of Microcrystalline Cellulose, about 51 %w of Spray Dried Mannitol, about 7 %w of Polyplasdone XL (super disintegrate), about 3% w of Poloxamer 407, about 1.5 %w of Citric Acid Monohydrate, about 1.0 %w of Cabosil M5P (fumed silica), and about 1.5 %w of Magnesium Stearate.

68. The use of claim 36, wherein the pharmaceutical composition comprises up to about 17.5%w of Bumetanide Dibenzylamide, about 9.9 %w of Lauroyl Plyoxyl-32 Glycerides, about 9.9 %w of Sorbitan Ester, about 54.3 %w of Polyplasdone XL (super disintegrate), about 0.5% w of Poloxamer 407, about 0.7 %w of Citric Acid Monohydrate, about 2.0 %w of Cabosil M5P (fumed silica), about 14.8 %w of Neusilin US2 (magnesium aluminometasilicate), and about 0.5 %w of Magnesium Stearate.

69. The use of claim 36, wherein the pharmaceutical composition comprises a vehicle composition comprising 55 Polyethylene Glycol 400 (PEG-400) in water, or 41 % PEG-400, 12 % ethanol, 47 % water or 45 % PEG-400, 10 % DMSO, 45 % water, or 31 % PEG-400, 31 % Tetraglycol, 15 % Caprylocaproyl Polyoxylglycerides, 23 % water, or 30 % PEG-400, 10 % N-Methyl Pyrrolidone, 10 % DMSO, 50 % water, or 25 % PEG-400, 10 % DMSO, 20 % Tetraglycol, 45 % water, or 20 % Ethanol in water, or 20% Hydroxypropyl-β-Cyclodextrin in water, or 11% DMSO, 22% PEG-400, 22% Tetraglycol, 44 % water, or 44 % PEG-400, 0.4 % Poloxamer-188, 22 % N-Methyl pyrrolidone, 33 % water, or 20 % PEG-400, 15 % Hydroxypropyl-β-Cyclodextrin in water, or 40 % PEG-400, 20 % Propylene Glycol, 5% Ethanol, and 35% water.

70. The use of claim 36, wherein the pharmaceutical composition comprises about 28 g of Bumetanide Dibenzylamide, and about 3 ml of a solvent, wherein 50 g of solvent comprises about 5g of Caprylocaproyl Polyoxylglycerides, about 10g of Propylene Glycol, about 28.5g of PEG-400, about 0.5g of Vitamin E TPGS, about 1g of Ethanol, and about 4.5g of water.

71. The use of any one of the claims 36-70, wherein the pharmaceutical composition is an oral capsule.

72. The use of any one of the claims 36-70, wherein the pharmaceutical composition is a nasal solution.

73. The use of any one of the claims 36-70, wherein the pharmaceutical composition is a rectal gel.

74. The use of any one of the claims 36-70, wherein the pharmaceutical composition is a rectal paste.

75. The use of any one of the claims 36-70, wherein the pharmaceutical composition is a sublingual tablet.

76. The use of any one of the claims 36-70, wherein the pharmaceutical composition is an injectable composition.

77. The use of any one of the claims 36-70, wherein the administration of the patient with the pharmaceutical composition is done orally.

78. The use of any one of the claims 36-70, wherein the administration of the patient with the pharmaceutical composition is done intranasally.

79. The use of any one of the claims 36-70, wherein the administration of the patient with the pharmaceutical composition is done intrarectally.

80. The use of any one of the claims 36-70, wherein the administration of the patient with the pharmaceutical composition is done sublingually.

81. The use of any one of the claims 36-70, wherein the administration of the patient with the pharmaceutical composition is done subcutaneously.

82. The use of any one of the claims 36-70, wherein the administration of the patient with the pharmaceutical composition is done intramuscularly.

83. A pharmaceutical composition of any one of the claims 1-35, comprising Bumetanide Dibenzylamide and one or more organic anion transport (OAT) inhibitors.

84. The pharmaceutical composition of claim 83, wherein the one or more OAT inhibitors are competitive antagonists.

85. The pharmaceutical composition of claim 84 or 83, wherein the Bumetanide Dibenzylamide and the one or more OAT inhibitors are formulated with different release profiles.

86. The pharmaceutical composition of claim 85, wherein at least one OAT inhibitor is formulated to be released prior to release of the Bumetanide Dibenzylamide.

87. The pharmaceutical compositon of claim 86, wherein at least one OAT inhibitor is formulated to be released prior to the Bumetanide Dibenzylamide achieving maximum plasma concentration (C_{max}) in a patient receving the composition.

88. The pharmaceutical composition of any one of claims 83 to 87, wherein the one or more OAT inhibitor is sleected from the group consisting of probenecid, aspirin, ibuprofen, acetylsalicylic acid, diclofenac, aspartame, and valproic acid.

89. A pharmaceutical composition of any one of the claims 1-35, comprising Bumetanide Dibenzylamide in a self-emulsifying drug delivery system (SEDDS).

90. The pharmaceutical composition of claim 89, wherein the SEDDS further comprises an isotropic mixture of oils, solubilizers, surfactants, and co-solvents.

91. A pharmaceutical compositon comprising Bumetanide Dibenzylamide in an oral lymphatic targeted formulation.

92. A pharmaceutical compositon of any one of the claims 1-35, comprising:

Bumetanide Dibenzylamide,

Polyoxyl 35 Castor Oil (Kolliphor EL),

Glyceryl Monolinoleate (Maisine CC),

Soybean Oil, and

Ethanol.

93. The composition of claim 91 or 92, comprising: about 1 to 2 w/w% Bumetanide Dibenzylamide, about 30 to 35 w/w% Polyoxyl 35 Castor Oil (Kolliphor EL), about 30 to 35 w/w% Glyceryl Monolinoleate (Maisine CC), about 30 to 35 w/w% Soybean Oil, and about 2.5 to 5 w/w% Ethanol.

94. The composition of any one of claims 91 - 93, comprising: 1.7 w/w% Bumetanide Dibenzylamide, about 32.4 w/w% Polyoxyl 35 Castor Oil (Kolliphor EL), about 31.3 w/w% Glyceryl Monolinoleate (Maisine CC), about 31.3 w/w% Soybean Oil, and about 3.2 w/w% Ethanol.

95. A pharmaceutical composition of any one of the claims 1-35, comprising a prodrug of Bumetanide and one or more oral lymphatic targeting excipients.

96. The pharmaceutical composition of claim 95, wherein the prodrug of Bumetanide is an amide prodrug.

97. The pharmaceutical composition of claim 95 or 96, wherein the prodrug of Bumetanide is one or more of Bumetanide Dibenzylamide, Bumetanide Diethylamide, and Bumetanide Morpholinoamide.

98. The pharmaceutical composition of any one of claims 95 - 97, comprising alkoxylated castor oil.

99. The pharmaceutical composition of any one of claims 95 - 97, comprising Polyoxyl 35 Castor Oil (Kolliphor EL).

100. The pharmaceutical composition of any one of claims 95 - 99, comprising one or more of a mono-, di-, and triglyceride.

101. The pharmaceutical composition of any one of claims 95 - 100, comprising Glyceryl Monolinoleate (Maisine CC).

102. The pharmaceutical composition of any one of claims 95 - 101, comprising a fixed oil.

103. The pharmaceutical compositon of any one of claims 95 - 102, comprising soybean oil.

104. The pharmaceutical composition of any one of claims 95 - 103, comprising a water soluable solvent.

105. The pharmaceutical composition of any one of claims 95 - 104, comprising ethanol.

106. The use of any one of the claims 36 - 81, wherein the pharmaceutical composition comprises up to 17.5 %w of Bumetanide Dibenzylamide, about 20 %w solublizer, and about 15 %w absorbant.

107. Use of a compound or composition as defined in any one of claims 1- 106 in the manufacture of a medicament for the treatment of epilepsy.

108. Use of a compound or composition as defined in any one of claims 1- 106 in the manufacture of a medicament for the treatment of a seizure disorder.

109. Use of a compound or composition as defined in any one of claims 1- 106 in the manufacture of a medicament for the treatment of Alzheimer's Disease.