**[0006]** In certain aspects and embodiments as described herein, the formulations as described herein may have certain surprising features and advantages that could not have been predicted prior to the present disclosure. For example, formulations of the instant disclosure may be able to support a dose of an active ingredient such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof) that is surprisingly higher than many prior art formulations and/or which produce surprisingly higher ocular tissue concentrations. The dose of active ingredient or agent used in the formulations described herein may be selected based on various criteria, including the amount that the formulation can support, the desired dose for various therapeutic applications, etc. In this regard, in some examples the active agent (such as for ophthalmic administration) may be at least about 0.05 wt%, or at least about 0.08 wt%, or at least about 0.09 wt%, or at least about 0.1 wt%, or at least about 0.15 wt%, or at least about 0.2 wt%, or at least about 0.3 wt%, or at least about 0.4 wt%, or at least about 0.5 wt%, or at least about 0.6 wt%, or at least about 0.7 wt%, or at least about 0.8 wt%, or at least about 0.9 wt%, or at least about 1.0 wt%, or at least about 1.5 wt%, or at least about 2 wt%, or at least about 3 wt%, or at least about 4 wt%, or at least about 5 wt%, or between 0.05 and 5 wt%, or between 0.05 and 0.5 wt%, or between 0.05 and 0.2 wt%, or between 0.08 and 0.12 wt%, or between 0.1 and 0.5 wt%, or between 0.5 and 1 wt%, or between 0.5 and 1.5 wt%, or between 1 and 5 wt%, or between 2 and 4 wt%, or between 4 and 6 wt% of the formulation.

**[0007]** In some examples the formulation has nanomicelles with a relatively increased entrapment efficiency; in such embodiments the active agent (such as brinzolamide, latanoprost, brimonidine, or bosentan (or pharmaceutically acceptable salts, prodrugs or variants thereof) for ophthalmic administration) may be at least about 0.05 wt%, or at least about 0.08 wt%, or at least about 0.09 wt%, or at least about 0.1 wt%, or at least about 0.15 wt%; or at least about 0.2 wt%, or at least about 0.3 wt%, or at least about 0.4 wt%, or at least about 0.5 wt%, or at least about 0.6 wt%, or at least about 0.7 wt%, or at least about 0.8 wt%, or at least about 0.9 wt%, or at least about 1.0 wt%, or at least about 1.5 wt%, or at least about 2 wt%, or at least about 3 wt%, or at least about 4 wt%, or at least about 5 wt%, or between 0.05 and 5 wt%, or between 0.05 and 0.5 wt%, or between 0.05 and 0.2 wt%, or between 0.08 and 0.12 wt%, or between 0.1 and 0.5 wt%, or between 0.5 and 1 wt%, or between 0.5 and 1.5 wt%, or between 1

and 5 wt%, or between 2 and 4 wt%, or between 4 and 6 wt% of the formulation and is present in nanomicelles of the formulation.

**[0008]** In certain aspects and examples, the formulations of the disclosure are surprisingly effective in dissolving and/or delivering active ingredients (such as brinzolamide, latanoprost, brimonidine, or bosentan (or pharmaceutically acceptable salts, prodrugs or variants thereof)) without a need for organic solvents (such as propylene glycol) that can be an irritant when included in ophthalmic formulations.

**[0009]** In some examples, the formulations of the present disclosure are surprisingly stable at high temperatures, for example, temperatures above about 40 degrees C. In some examples the nanomicellular nature of some formulations described herein allow for improved ocular tissue distribution. In certain examples, formulations as described herein are particularly suitable for anterior eye delivery, or posterior eye delivery, or anterior and posterior eye delivery. Moreover, the formulations of certain aspects and embodiments of the disclosure may have the surprising advantage of being adaptable to facilitate delivery of active agents having various sizes or properties; for example, in certain examples in formulations that include a polyoxyl castor oil, HCO-60 could be used for active agents having relatively small molecule sizes and HCO-80 and/or HCO-100 could be used for relatively larger sized active agents.

**[0010]** Accordingly, in a first example provided is an ophthalmic formulation that includes an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), a polyoxyl lipid or fatty acid and a polyalkoxylated alcohol. In some examples the formulations includes nanomicelles. In some examples the polyoxyl lipid or fatty acid is a polyoxyl castor oil. In some examples, the polyoxyl lipid or fatty acid is one or more selected from HCO-40, HCO-60, HCO-80 or HCO-100. In some examples the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-40, HCO-60, HCO-80 or HCO-100) is present between 1 and 6%; or 2 and 6%; or 2 and 6%; or 3 and 6%; or 4 and 6%; or 2 and 5%; or 3 and 5%; or 3 and 5%; or 2 and 6%; or about 4%; or greater than 0.7%; or greater than 1%, or greater than 1.5%; or greater than 2%; or greater than 3%; or greater than 4% by weight of the formulation. In some

examples the polyoxyl lipid is HCO-60. In some embodiments the polyoxyl lipid is HCO-80. In some embodiments the polyoxyl lipid is HCO-100. In some examples, the formulation includes a polyalkoxylated alcohol that is octoxynol-40. In some examples, the formulation includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%; or between 0.005 and 3%; or 0.005 and 2%; or 0.005 and 1%; or 0.005 and 0.5%; or 0.005 and 0.1%; or 0.005 and 0.05%; or 0.008 and 0.02%; or about 0.01% by weight of the formulation.

**[0011]** As used herein, the term "polyoxyl lipid or fatty acid" refers to mono- and diesters of lipids or fatty acids and polyoxyethylene diols. Polyoxyl lipids or fatty acids may be numbered ("n") according to the average polymer length of the oxyethylene units (e.g., 40, 60, 80, 100) as is well understood in the art. The term "n $\geq$ 40 polyoxyl lipid" means that the ploy oxyl lipid or fatty acid has an average oxyethylene polymer length equal to or greater than 40 units. Stearate hydrogenated castor oil and castor oil are common lipids/fatty acids commercially available as polyoxyl lipids or fatty acid, however, it is understood that any lipid or fatty acid could be polyoxylated to become a polyoxyl lipid or fatty acid as contemplated herein. Examples of polyoxyl lipid or fatty acids include without limitation HCO-40, HCO-60, HCO-80, HCO-100, polyoxyl 40 stearate, polyoxyl 35 castor oil, and the like.

**[0012]** In some examples of any of the compositions and methods described herein, the average polymer length of the oxyethylene units of a polyoxyl lipid or fatty acid is longer for a relatively larger active ingredient and is shorter for a relatively smaller active ingredient; for example in some examples in which the active ingredient is brinzolamide, the polyoxyl lipid is HCO-60 and in some examples where the active ingredient is bosentan (which is larger than brinzolamide) the polyoxyl lipid is HCO-80 or HCO-100.

**[0013]** As used herein, the term "micelle" or "nanomicelle" refers to an aggregate (or cluster) of surfactant molecules. Micelles only form when the concentration of surfactant is greater than the critical micelle concentration (CMC). Surfactants are chemicals that are amphipathic, which means that they contain both hydrophobic and hydrophilic groups. Micelles can exist in different shapes, including spherical, cylindrical, and discoidal. A micelle comprising at least two different molecular species is a mixed micelle. In some examples,

ophthalmic compositions of the present disclosure include an aqueous, clear, mixed micellar solution.

**[0014]** In another example, provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), and a n≥ 40 polyoxyl lipid or fatty acid. In some examples the formulation includes nanomicelles. In some examples the polyoxyl lipid or fatty acid is a polyoxyl castor oil. In some examples, the polyoxyl lipid or fatty acid is one or more selected from HCO-40, HCO-60, HCO-80 or HCO-100. In some examples the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-40, HCO-60, HCO-80 or HCO-100) is present between 0.5 and 2%, or 0.7 and 2%, or 1 and 6%, or 2 and 6%, or 2 and 6%, or 3 and 6%, or 4 and 6%, or 2 and 5%, or 3 and 5%, or 3 and 5%, or 2 and 6%, or about 4%, or greater than 0.7%, or greater than 1%, or greater than 1.5%, or greater than 2%, or greater than 3%, or greater than 4% by weight of the formulation. In some examples the polyoxyl lipid is HCO-60. In some examples the polyoxyl lipid is HCO-80. In some embodiments the polyoxyl lipid is HCO-100.

**[0015]** In some examples, the formulation further includes polyalkoxylated alcohol. In some examples, the formulation further includes polyalkoxylated alcohol that is octoxynol-40. In some examples, the formulation includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%, or between 0.005 and 3%, or between 0.005 and 2%, or between 0.005 and 1%, or between 0.005 and 0.5%, or between 0.005 and 0.1%, or between 0.005 and 0.05%, or between 0.008 and 0.02%, or between 0.01 and 0.1%, or between 0.02 and 0.08%, or between 0.005 and 0.08%, or about 0.05%, or about 0.01% by weight of the formulation.

**[0016]** In another example, provided is an ophthalmic formulation, that includes an active ingredient such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), and a polyoxyl lipid or fatty acid; wherein said polyoxyl lipid or fatty acid is present in an amount equal to or greater than 1 wt% of said formulation. In another example, provided is an ophthalmic formulation, that includes an active ingredient such as brinzolamide, latanoprost, brimonidine,

bosentan, or mixtures of any two or more thereof, and a polyoxyl lipid or fatty acid; wherein said polyoxyl lipid or fatty acid is present in an amount equal to or greater than 0.05 wt% of said formulation. In some examples the formulations include nanomicelles. In some examples the polyoxyl lipid or fatty acid is a polyoxyl castor oil. In some examples, the polyoxyl lipid or fatty acid is one or more selected from HCO-40, HCO-60, HCO-80 or HCO-100. In some examples the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-60, HCO-80 or HCO-100) is present between 0.5 and 2%, or 0.7 and 2%, or between 1 and 6%, or 2 and 6%, or 2 and 6%, or 3 and 6%, or 4 and 6%, or 2 and 5%, or 3 and 5%, or 3 and 5%, or 2 and 6%, or about 4%, or greater than 1.5%, or greater than 2%, or greater than 3%, or greater than 4% by weight of the formulation. In some examples the polyoxyl lipid is HCO-40. In some examples the polyoxyl lipid is HCO-60. In some examples the polyoxyl lipid is HCO-80. In some examples the polyoxyl lipid is HCO-100.

**[0017]** In some examples, the formulation further includes polyalkoxylated alcohol. In some examples, the formulation further includes polyalkoxylated alcohol that is octoxynol-40. In some examples, the formulation includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%, or between 0.005 and 3%, or between 0.005 and 2%, or between 0.005 and 1%, or between 0.005 and 0.5%, or between 0.005 and 0.1%, or between 0.005 and 0.05%, or between 0.008 and 0.02%, or between 0.01 and 0.1%, or between 0.02 and 0.08%, or between 0.005 and 0.08%, or about 0.05%, or about 0.01% by weight of the formulation.

**[0018]** In another example, provided is an ophthalmic formulation, that includes an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), and a polyoxyl lipid or fatty acid; wherein said formulation comprises nanomicelles. In some examples the polyoxyl lipid or fatty acid is a polyoxyl castor oil. In some examples the polyoxyl lipid or fatty acid is one or more selected from HCO-40, HCO-60, HCO-80 or HCO-100. In some examples the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-40, HCO-60, HCO-80 or HCO-100) is present between 0.5 and 2%, or 0.7 and 2%, or between 1 and 6%, or 2 and 6%, or 2 and 6%, or 3 and 6%, or 4 and 6%, or 2 and 5%, or 3 and 5%, or 3 and 5%, or 2 and 6%, or about 4%, or greater than 0.7%, or greater than 1%, or greater than 1.5%, or

greater than 2%, or greater than 3%, or greater than 4% by weight of the formulation. In some examples the polyoxyl lipid is HCO-40. In some examples the polyoxyl lipid is HCO-60. In some examples the polyoxyl lipid is HCO-80. In some examples the polyoxyl lipid is HCO-100.

**[0019]** In some examples, the formulation further includes polyalkoxylated alcohol. In some examples, the formulation further includes polyalkoxylated alcohol that is octoxynol-40. In some embodiments, the formulation includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%, or between 0.005 and 3%, or between 0.005 and 2%, or between 0.005 and 1%, or between 0.005 and 0.5%, or between 0.005 and 0.1%, or between 0.005 and 0.05%, or between 0.008 and 0.02%, or between 0.01 and 0.1%, or between 0.02 and 0.08%, or between 0.005 and 0.08%, or about 0.05%, or about 0.01% by weight of the formulation.

**[0020]** In another example provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), 1-5 wt% of one or more selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.002-4 wt% octoxynol-40.

**[0021]** In another example, provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), 1-5 wt% of one or more selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.005-3 wt% octoxynol-40.

**[0022]** In yet another example, provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), 1-5 wt% of one or more selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.005-2 wt% octoxynol-40.

**[0023]** In one example, provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), 1-5 wt% of one or more selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.005-1 wt% octoxynol-40.

**[0024]** In a further example provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), about 4 wt% of HCO-60 and about 0.01 wt% octoxynol-40.

**[0025]** In another example provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), 0.7-1.5 wt% of one or more selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.002-4 wt% octoxynol-40.

**[0026]** In another example, provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), 0.7-1.5 wt% of one or more selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.005-3 wt% octoxynol-40.

**[0027]** In yet another example, provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), 0.7-1.5 wt% of one or more selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.005-2 wt% octoxynol-40.

**[0028]** In one example, provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), 0.7-1.5 wt% of one or more

selected from the group consisting of HCO-40, HCO-60, HCO-80 and HCO-100; and about 0.05 wt% octoxynol-40.

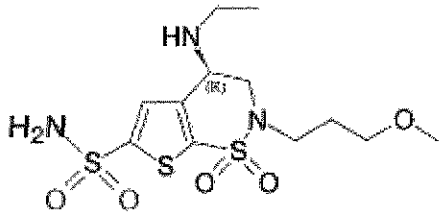
**[0029]** In a further example provided is an ophthalmic formulation, comprising an active agent such as brinzolamide, latanoprost, brimonidine, bosentan, or mixtures of any two or more thereof (or pharmaceutically acceptable salts, prodrugs or variants thereof), about 1 wt% of HCO-60 and about 0.05 wt% octoxynol-40.

**[0030]** In various examples of any of the aspects and examples described herein, the formulation includes nanomicelles.

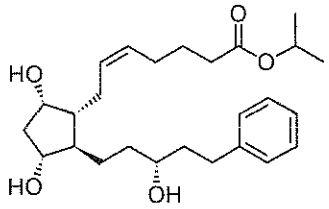
**[0031]** In some examples described herein, the formulation includes a polyoxyl lipid or fatty acid. In some examples the polyoxyl lipid or fatty acid is a polyoxyl castor oil. In some examples, the polyoxyl lipid or fatty acid is one or more selected from HCO-40, HCO-60, HCO-80 or HCO-100. In some examples the polyoxyl lipid or fatty acid (such as a polyoxyl castor oil such as HCO-60, HCO-80 or HCO-100) is present between 0.5 and 2%, or 0.7 and 2%, or 1 and 6%, or 2 and 6%, or 2 and 6%, or 3 and 6%, or 4 and 6%, or 2 and 5%, or 3 and 5%, or 3 and 5%, or 2 and 6%, or about 4%, or greater than 0.7%, or greater than 1%, or greater than 1.5%, or greater than 2%, or greater than 3%, or greater than 4% by weight of the formulation. In some examples the polyoxyl lipid is HCO-40. In some examples the polyoxyl lipid is HCO-60. In some examples the polyoxyl lipid is HCO-80. In some examples the polyoxyl lipid is HCO-100.

**[0032]** In some examples of the aspects and embodiments disclosed herein, the formulation includes a polyalkoxylated alcohol. In some examples, the formulation includes a polyalkoxylated alcohol that is octoxynol-40. In some examples, the formulation includes a polyalkoxylated alcohol (such as octoxynol-40) present between 0.002 and 4%, or between 0.005 and 3%, or between 0.005 and 2%, or between 0.005 and 1%, or between 0.005 and 0.5%, or between 0.005 and 0.1%, or between 0.005 and 0.05%, or between 0.008 and 0.02%, or between 0.01 and 0.1%, or between 0.02 and 0.08%, or between 0.005 and 0.08%, or about 0.05%, or about 0.01% by weight of the formulation.

**[0033]** In some examples, the active ingredient is a carbonic anhydrase inhibitor such as brinzolamide, methazolamide, dorzolamide, topiramate, punicalin, punicalagin, granatin B, gallagyldilactone, casuarinin, pedunculagin, tellimagrandin I, and the like, as well as pharmaceutically acceptable salts, prodrugs or variants thereof. In some examples, the carbonic anhydrase inhibitor is brinzolamide, which has the structure:

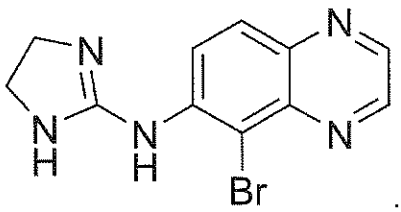


**[0034]** In some examples, the active agent is a prostaniod such as latanoprost, having the structure:



Latanoprost is also known by the brand name of Xalatan manufactured by Pfizer.

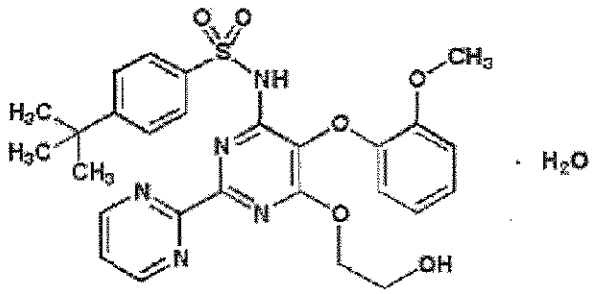
**[0035]** In some examples, the active agent is an $\alpha_2$ adrenergic agonist, such as brimonidine, having the structure:



Brimonidine is available as eye drops under the brand names Alphagan and Alphagan-P and as a gel, under the brand name Mirvaso.

**[0036]** In some examples, the active ingredient is an endothelin receptor antagonist such as bosentan (that belongs to a class of highly substituted pyrimidine derivatives, with no

chiral centers), ambrisentan, sitaxsentan, and the like. In some examples, the endothelin receptor antagonist is bosentan, which has the following structure:




**[0037]** As used herein, the term "pharmaceutically acceptable salts" includes salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

**[0038]** Thus, the compounds contemplated for use in the practice of the present disclosure may exist as salts, such as with pharmaceutically acceptable acids. The present disclosure includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

**[0039]** In addition to salt forms, the present disclosure provides compounds which are in a prodrug form. The term "prodrugs" and the like refer, in the usual and customary sense, to compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Additionally, prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an ex vivo environment.

**[0040]** As used herein, the terms"pharmaceutically acceptable excipient," "pharmaceutically acceptable carrier" and the like refer, in the usual and customary sense, to a substance that aids the administration of an active agent to and absorption by a subject and which can be included in the compositions of the present disclosure without causing a significant adverse toxicological effect on the patient. The term "adverse toxicological effect" and the like refer, in the usual and customary sense, to an indication that a candidate excipient should not be used, as judged by a medical or veterinary practitioner or as known in the art. Unless indicated to the contrary, the terms "drug," "active agent," "active ingredient," "therapeutically active agent," "therapeutic agent" and like are used synonymously. Non limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, solutions of pharmaceutically acceptable salts (e.g., Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, polyethylene glycol, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react

with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

**[0041]** The instant disclosure further relates to treating or preventing ocular diseases or disorders, for example by local administration of the formulations as described herein.

**[0042]** A patient or subject to be treated by any of the compositions or methods of the present disclosure can mean either a human or a non-human animal. In an example, the present disclosure provides methods for the treatment of an ocular disease in a human patient in need thereof. In an example, the present disclosure provides methods for the treatment of an inflammatory ocular disease in a human patient in need thereof. In another example, the present disclosure provides methods for the treatment of an ocular disease in a veterinary patient in need thereof, including, but not limited to dogs, horses, cats, rabbits, gerbils, hamsters, rodents, birds, aquatic mammals, cattle, pigs, camelids, and other zoological animals.

**[0043]** In some examples of the compositions and methods disclosed herein, the active agent comprises a combination of two or more different active ingredients (or pharmaceutically acceptable salts, prodrugs or variants thereof). In some examples the active agent comprises a carbonic anhydrase inhibitor (such as brinzolamide) and at least one second active agent such as those described in PCT Publication No. WO 2014/032026 (incorporated by reference herein in its entirety). In some examples, the active agent comprises an endothelin receptor antagonist (such as bosentan) and at least one second active agent such as those described in PCT Publication No. WO 2014/032026 (incorporated by reference herein in its entirety).

**[0044]** In some examples the active agent includes a carbonic anhydrase inhibitor and an endothelin receptor antagonist. In some examples the active agent includes a carbonic anhydrase inhibitor and a resolvin. In some examples the active agent includes an endothelin receptor antagonist and a resolvin. In some examples the active agent includes a carbonic anhydrase inhibitor and a prostaniod. In some examples the active agent includes an endothelin receptor antagonist and a prostaniod. In some examples the active agent includes a carbonic anhydrase inhibitor and an $\alpha_2$ adrenergic agonist. In some examples, the active agent includes a an endothelin receptor antagonist and an $\alpha_2$ adrenergic agonist.

**[0045]** The term "treating" refers to: preventing a disease, disorder or condition from occurring in a cell, a tissue, a system, animal or human which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; stabilizing a disease, disorder or condition, i.e., arresting its development; and/or relieving one or more symptoms of the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

**[0046]** As used herein, a therapeutic that "prevents" a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

**[0047]** As used herein, the terms "ocular disease," "ocular condition," "eye disease," and "eye condition" refer to diseases/conditions of the eye(s) that can be sight threatening, lead to eye discomfort, and may signal systemic health problems.

**[0048]** As used herein, the term "anterior segment disease" refers to all disorders that affect the eye surface, anterior chamber, iris and ciliary body and lens of the eye. The eye surface is composed of the cornea, conjunctiva, eyelids, lacrimal and meibomian glands, and the interconnecting nerves.

**[0049]** As used herein, the terms "posterior segment eye disease" and "back-of-the-eye disease" refer to all disorders that affect the posterior segment of the eye. A posterior eye disease is a disease which primarily affects a posterior ocular site such as choroid or sclera, vitreous, vitreous chamber, retina, optic nerve, and blood vessels and nerves which vascularize or innervate a posterior ocular site.

**[0049A]** In one aspect, there is provided use of a formulation as described herein in the manufacture of a medicament for treating or preventing an ocular disease or condition.

**[0049B]** In another aspect, there is provided use of a formulation as described herein in the manufacture of a medicament for treating or preventing an ocular disease or condition.

**[0050]** Accordingly, in one example, provided is a method treating or preventing an ocular disease or condition, that includes locally administering a formulation of any of the aspects or embodiments as disclosed herein. In some examples, the ocular disease is an anterior segment disease. In some examples, the ocular disease is a posterior segment disease. In some examples, the ocular disease is one or more selected from the group consisting of primary open angle glaucoma, primary angle closure glaucoma, ocular hypertension,

inflammatory glaucoma, drug-induced glaucoma, diabetic retinopathy (DR), optic neuritis, retrobulbar neuritis, and macular pucker. In one example, the ocular disease is primary open angle glaucoma. In one example, the ocular disease is primary close angle glaucoma. In one example the ocular disease is optic neuritis. In one example the ocular disease is diabetic retinopathy.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

### Active Agents

**[0051]** In accordance various aspects and embodiments of the methods and compositions provided herein, an active agent can be any agent capable of affecting a biological process (e.g., brinzolamide, latanoprost, brimonidine, or bosentan). Active agents (the term active ingredient is used herein interchangably with the term active agent) include drugs, hormones, cytokines, toxins, therapeutic agents, vitamins and the like. In some embodiments an active agent in accordance with the aspects and embodiments disclosed herein is an agent capable of, or approved for, treating or preventing a disease or condition, for example in some embodiments an active agent is capable of, or approved for, treating or preventing an ocular disease or condition.

**[0052]** In some embodiments, the active agent is a carbonic anhydrase inhibitor such as brinzolamide, methazolamide, dorzolamide, topiramate, punicalin, punicalagin, granatin B, gallagyldilactone, casuarinin, pedunculagin, tellimagrandin I, and the like, as well as pharmaceutically acceptable salts, prodrugs or variants thereof.

**[0053]** In some embodiments, the active agent is an endothelin receptor antagonist that belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers. Exemplary endothelin receptor antagonists include bosentan, ambrisentan, sitaxsentan, and the like, as well as pharmaceutically acceptable salts, prodrugs or variants thereof.

**[0054]** In some embodiments, the active agent is a prostanoid such as latanoprost, travoprost, tafluprost, unaprostone, bimatoprost, and the like, as well as pharmaceutically acceptable salts, prodrugs or variants thereof.

17. The ophthalmic formulation of claim 1, wherein said polyoxyl lipid comprises one or more selected from the group consisting of HCO-40, HCO-60, HCO-80, HCO-100, polyoxyl 40 stearate and polyoxyl 35 castor oil and is present in an amount between 0.5-1.5 wt% of the formulation; and said polyalkoxylated alcohol is Octoxynol-40 and is present in an amount between 0.02 and 0.1 wt% of the formulation; and the active agent is present in an amount between 0.05 and 0.2 wt% of the formulation.

18. The ophthalmic formulation of claim 1, wherein said formulation comprises nanomicelles.

19. The ophthalmic formulation of any one of claims 1 – 18, wherein said active agent is *brinzolamide*.

20. The ophthalmic formulation of any one of claims 1 – 18, wherein said active agent is bosentan.

21. The ophthalmic formulation of any one of claims 1 – 18, wherein said active agent is latanoprost.

22. The ophthalmic formulation of any one of claims 1 – 18, wherein said active agent is brimonidine.

23. Use of a formulation of any one of claims 1 – 22 in the manufacture of a medicament for treating or preventing an ocular disease or condition.

24. Use of a formulation of claim 17 in the manufacture of a medicament for treating or preventing an ocular disease or condition.