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(54) **Title**: NOVEL OPHTHALMIC COMPOSITIONS

(57) **Abstract**: An ophthalmic solution comprising therapeutically effective amount of a prostaglandin or its analog and water sol-

NOVEL OPHTHALMIC COMPOSITIONS

The present invention relates to a novel ophthalmic solution prostaglandin or its analogs alone or in combination with other antiglaucoma agents.

BACKGROUND OF THE INVENTION

Prostaglandins are well known active substances administered to humans or animals via the topical route in the form of ophthalmic solutions for the treatment of glaucoma. The prostaglandins may also be used in combination with a second anti-glaucoma agent such as a beta-blocker, a carbonic anhydrase inhibitor or an alpha-adrenergic agonist.

Prostaglandin or its analogs, particularly the ester derivatives such as latanoprost, travoprost or the amide derivatives such as bimatoprost have notoriously low water solubility. The use of compounds which exert a surfactant like activity in to solubilize them is therefore, very common. Currently available prostaglandin ophthalmic solution, are found to contain a typical surfactant or a quaternary ammonium salt which is known to have a surfactant like activity apart from preservative property. Representative examples of typical surfactants incorporated in the ophthalmic solutions of prostaglandin analogs alone or in combination with other antiglaucoma agent, like for example, beta adrenergic blocking agent or alpha adrenergic blocking agent or any other active agent, are tabulated here:

Product	Active Ingredient	Surfactant
Xalatan®	Latanoprost	Benzalkonium chloride
Travatan Z®	Travoprost	polyoxyl 40 hydrogenated castor oil (Cremphore)
Xalacom®	Latanoprost and timolol	Benzalkonium chloride
Lumigan®	Bimatoprost	Benzalkonium chloride
Ganfort®	Bimatoprost and timolol	Benzalkonium chloride
Duotrav®	Travoprost and timolol	Benzalkonium chloride
Rescula®	Unoprostone isopropyl	Polyoxyethylene-20-sorbitan-monooleate

Apart from the approved products, the patent literature also represents numerous efforts of solubilizing prostaglandins with the help of solubilizers such as polyoxyethylene-20-sorbitan-monooleate, polyoxy stearates like Solutol® with or without other antiglaucoma agent like beta adrenergic blocking agent. Below is a list of patent documents that

disclose the use of surfactant in a prostaglandin ophthalmic solution alone or in combination with other antiglaucoma agent.

Product disclosed in Literature	Prostaglandin	Surfactant
US7074827	Latanoprost	Polyoxyethylene-20-sorbitan-monooleate
US20100201720	Prostaglandin	Solutol
WO/2009/145356	Tafluprost	Polyoxyethylene-20-sorbitan-monooleate
US20030018079	Latanoprost and Timolol	Polyoxyethylene-20-sorbitan-monooleate and Benzalkonium chloride

Generally, the formulation development of ophthalmic solution of prostaglandin or their combination with other active ingredient, over the years, is directed towards achieving a stable composition particularly in view of the fact that prostaglandins are also known to chemically unstable. Further, the literature provides evidences that the prostaglandins were associated with an adsorption problem to the poly-ethylene multidose containers. Some solutions to solve these problems are described in patent documents such as, for example, United States patent number US 6,235,781 which discloses that use of a surfactant to prevent the adsorption of prostaglandin analogues on to the plastic containers. The inventor of the present invention also faced and tackled this problem of adsorption of prostaglandin as described in WO 2009/084021. It was found out by inventors that a micro-emulsion formulation of prostaglandin containing polyoxy hydroxystearate (commonly known as Solutol HS) provides the solution to stability problem associated with adsorption. Another patent application, namely, United States Patent number US 20090234013A1, discloses a solution which include a therapeutic agent and a relatively low amount of surfactant for providing higher bioavailability of prostaglandin such as travoprost. Thus, this prior art as well teaches to include some amount of a surfactant such as ethoxylated and/or hydrogenated vegetable oil. This implies that the surfactant is always desirable to make the solution however it is preferable to keep it as low as possible.

Now, the inventors surprisingly and unexpectedly found that the prostaglandin analogs can be effectively formulated into an ophthalmic solution vehicle having a water soluble excipient(s) dissolved in the vehicle, wherein the ophthalmic solution is free of a surfactant. When the efficacy of the ophthalmic solution was compared with an ophthalmic solution comprising a surfactant, it was found that the ophthalmic solution provided equivalent or improved efficacy in reducing the intraocular pressure. Particularly, the ophthalmic solution of present invention was found to provide equivalent efficacy at half the dose compared to the marketed product available under the tradename of Xalatan® when tested in animals. This achievement of equivalent efficacy at half the dose of latanoprost was indeed unexpected and surprising. It was further found that the % intraocular pressure reduction at 12 hour time point, which apparently provides a peak IOP reduction was higher compared to the % intraocular pressure reduction at 12 hours, for Xalatan® which is a latanoprost ophthalmic solution having benzalkonium chloride as a surfactant. This effect of improved efficacy inspite of the absence of a surfactant, was also observed when the ophthalmic solution of the present invention was made of a prostaglandin or its analog and another antiglaucoma agent like a beta adrenergic blocking agent. The ophthalmic composition comprising prostaglandin or its nalog and a beta-adrenergic blocking agent that is free of surfactant, the composition remained stable and did not show any hazyness. The composition was clear on storage and was chemically stable.. Thus, the invention not only provided a physically stable composition comprising the two active ingredients, but also provided an ophthalmic composition that was more efficacious. Since the compositions are intended for ophthalmic purposes, it is always desirable that the compositions are devoid of excessive additives. Therefore, the present invention can be said to achieve not only the patient compliance but also achieved an improved efficacious composition.

Thus, the ophthalmic composition of the present invention comprises a combination of a prostaglandin and a beta-adrenergic blocking agent, characterized in that it does not use any surfactant or a surfactant preservative in a concentration that acts as a solubilizer such as those from alkyl quaternary ammonium surfactant like benzalkonium chloride,

benzdodecinium chloride and like and mixtures thereof. In one preferred embodiment, the ophthalmic composition includes a vehicle that is free of surfactants and added preservatives and is able to provide a beta-adrenergic blocking agent when administered topically such that effect is sustained for 24 hours, that is the ophthalmic composition is said to be suitable for once-a-day administration. Therefore, one of the embodiment of the present invention can be said to provide an ophthalmic composition comprising latanoprost and once-a-day composition of a beta-adrenergic blocking agent, wherein the composition is free of surfactant and optionally, free of added preservative and is found to be suitable for treating the affected eye of a glaucoma patient.

The ophthalmic solution of the present invention is free of a surfactant as well as free of anti-microbial preservatives defined by the class of quaternary ammonium compounds, organo-mercurials and substituted alcohol and phenols. It is known that these antimicrobials are often toxic to the sensitive tissues of the eye. The present invention thereofore fulfils the need of an ophthalmic solution which is stable as well having improved efficacy while not compromising on the antimicrobial activity. The present invention provides an ophthalmic solution comprising prostaglandins which obtains dual benefits of improved efficacy and avoidance of undesirable effects of the preservatives.

OBJECTS OF THE INVENTION

The object of the invention is to provide an ophthalmic solution that allows dose reduction of the prostaglandin while achieving equivalent efficacy.

The present invention relates to an ophthalmic solution comprising therapeutically effective amount of a prostaglandin analogue and another active ingredient, wherein the solution provides therapeutic effect sustaining for 24 hours i.e. to provide a once -a-day therapy.

The object of the present invention to provide a stable ophthalmic solution of prostaglandin analogs.

The object of the present invention to provide a stable ophthalmic solution of prostaglandin analogs and beta adrenergic active agents.

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