A fixed dose pharmaceutical composition comprises at least two anti-glaucoma agents and one or more pharmaceutically acceptable excipients.
TITLE:
Fixed Dose Pharmaceutical Composition

FIELD OF INVENTION:
The present invention relates to a fixed dose pharmaceutical composition comprising at least two anti-glaucoma agents, a process for preparing such a fixed dose pharmaceutical composition and the use of the said fixed dose pharmaceutical composition for the treatment of glaucoma.

BACKGROUND AND PRIOR ART:
Glaucoma is an ocular disorder characterized by elevated intraocular pressure, excavation of the optic nerve head and gradual loss of the vision field. An abnormally high intraocular pressure will have a generally detrimental effect on the eye; and there are clear indications that this is probably the main factor causing degenerative changes of the retina in glaucoma patients.

However, the pathophysiological mechanism underlying open-angle glaucoma is still unknown. If not treated successfully the disease will usually proceed to blindness sooner or later, its course towards that stage being characterized by a slow but progressive loss of vision.

In humans the IOP will normally be within the range of from 12 to 22 mm Hg. At higher values, e.g. exceeding 22 mm Hg, there is a risk that the eye may be affected. In a special form of glaucoma, the so-called low-tension glaucoma, lesions will occur at intraocular pressure levels which are generally regarded as physiological. Possibly this may be due to an increased pressure sensitivity of the eye of such an individual. Also the opposite type of phenomenon is known, i.e. some individuals may have in abnormally high intraocular pressure without any noticeable distinct defects in their vision field or optic nerve head. Such conditions are usually named "ocular hypertension".

Glaucoma treatments may be given by means of drugs, laser or surgery. In the case of drug treatments, the purpose is to lower the IOP or alternatively, the purpose may be to increase the flow of the aqueous humor which too will be a means of lowering the pressure.
Interest in prostaglandins as IOP reducing substances has been growing substantially for quite some time. The prostaglandin analogues are a group of compounds that have become the most frequently used ocular hypotensive drugs owing to their efficiency in reducing intraocular pressure and the low incidence rate and severity of adverse events, in particular in the absence of systemic side effects, especially in comparison to the beta-blockers.

Prostaglandins are ubiquitous local hormones that produce ocular inflammation and hypertension in high levels but in smaller amounts reduces IOP. Prostaglandins are potent ocular hypotensives as first line therapy for ocular hypertension and Primary Open-Angle Glaucoma (POAG) and such prostaglandins include latanoprost, travoprost, tafluprost, unoprostone and bimatoprost.

Tafluprost (1-methylethyl (5Z)-7-[(lR,2R,3R,5S)-2-[(lE)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxycyclopentyl]-5- heptenoate)24,3 is a 16-phenoxy analog of PGF2a, with a 15,15-difluoro substitution.21 It is presently available in two formulations, ie, with benzalkonium chloride (BAK) - Tapros® in Japan (Santen Pharmaceutical Co. Ltd., Osaka, Japan) and preservative-free in Europe, ie, Taflotan® (Santen Oy, Finland), both in 0.0015% (15 µg/mL) concentrations.

Systemic carbonic anhydrase inhibitors (CAI) have been a mainstay in the medical treatment of glaucoma. However, their use was associated by the relatively high incidence of systemic side effects, which led development of topical carbonic anhydrase inhibitors.

Such topical carbonic anhydrase inhibitors include dorzolamide and brinzolamide. Dorzolamide is the first topical carbonic anhydrase inhibitor with substantial ocular hypotensive efficacy to be
made available for clinical use. Dorzolamide has been found to be well tolerated and to reduce intraocular pressure (IOP) by 14% to 24% in adults.

![Dorzolamide](image)

Dorzolamide

Brinzolamide is described chemically as: (R)-(+) 4-Ethylamino-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno [3,2-c]-1,2-thiazine-6-sulfonamide-1,1-dioxide.

![Brinzolamide](image)

Brinzolamide

Acetazolamide is chemically described as N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide and has the following chemical structure.

![Acetazolamide](image)

Acetazolamide

Methazolamide is chemically described as N-[5-(aminosulfonyl)-3-methyl-1,3,4-thiadiazol-2(3H)-ylidene]acetamide.
"Ocular hypotensive effects of anti-glaucoma agents in mice" by Akaishi T, Odani-Kawabata, N Ishida, N Nakamura M. This article discloses that concomitant administration of timolol and tafluprost or of dorzolamide and tafluprost induced a significantly greater IOP reduction than that induced by either of the individual components.

Impact of prostaglandin-F (2alpha)-analogues and carbonic anhydrase inhibitors on central corneal thickness - a cross-sectional study on 403 eyes, Klin Monbl Augenheilkd, 2004 Sep; 221(9):753-6. This article discloses the separate use of prostaglandin-F (2alpha)-analogues and carbonic anhydrase inhibitors for the treatment of primary open angle glaucoma.

The inventors of the present invention have appreciated that although the above documents describe concomitant administration of a prostaglandin derivative with a carbonic anhydrase inhibitor, they do not provide or discuss the two types of drug in a form that provides adequate patient compliance by reducing the frequency of administration and costs of the medication.

Furthermore, prostaglandin derivatives act by lowering intraocular pressure by increasing uveoscleral outflow (the minor pathway for the removal of aqueous humour from the anterior chamber of the eye) and decreasing episcleral venous pressure and carbonic anhydrase inhibitors act by decreasing production of aqueous humour.

Glaucoma is a condition in which the trabecular meshwork which aids in the drainage of the aqueous fluid is affected or damaged thereby inhibiting or preventing the drainage of the aqueous fluid and building up intraocular pressure (IOP) further damaging the optic nerve thus impairing the vision.

The inventors of the present invention have further appreciated that, the combination of prostaglandin derivatives and carbonic anhydrase inhibitors may provide a complimentary mechanism of action as both are efficacious in reducing the IOP. Prostaglandin derivatives acts
by increasing the uveoscleral outflow of aqueous humor and carbonic anhydrase inhibitors act by reducing the aqueous humor production. Thus, the different mechanisms of action will lead to an additive effect in reducing the intraocular pressure.

The inventors of the present invention have further appreciated that, in the case of ocular medications administered in the form of eye drops the droplet size, number of doses administered per day and wastage of medicament during instillation are also important factors to consider. Furthermore, it has been appreciated that patients may tend to skip doses with concomitant administration of drugs, or because of side effects and/or due to extended dosing regimens, which may possibly lead to blindness.

The inventors of the present invention have appreciated the problems and shortfalls associated with the existing anti-glaucoma treatments and sought ways to address them.

OBJECT OF THE INVENTION:

An object of the present invention is to provide at least two anti-glaucoma agents in a form that provides improved patient compliance by decreasing the necessary frequency of administration and cost of the medication.

It is a further object to provide at least two anti-glaucoma agents in a form whereby medicament wastage is minimized, and where the side effects of concomitant administration are reduced.

Another object of the present invention is to provide at least two anti-glaucoma agents in a form having improved surface area and solubility, and also reduced dose.

Yet another object of the present invention is to provide a fixed dose pharmaceutical composition comprising at least two anti-glaucoma agents having a reduced dose.

SUMMARY OF THE INVENTION:

According to an aspect of the present invention, there is provided a fixed dose pharmaceutical composition comprising at least two anti-glaucoma agents and one or more pharmaceutically acceptable excipients.
Preferably, the anti-glaucoma agents comprise a carbonic anhydrase inhibitor. Preferably, the anti-glaucoma agents comprise a prostaglandin derivative. More preferably, the anti-glaucoma agents present in the composition comprise a carbonic anhydrase inhibitor and a prostaglandin derivative.

Preferably, the prostaglandin derivative is tafluprost. Preferably, the carbonic anhydrase inhibitor is dorzolamide, brinzolamide, acetazolamide or methazolamide. Preferably, the at least two anti-glaucoma agents comprise tafluprost and dorzolamide, tafluprost and brinzolamide, tafluprost and acetazolamide or tafluprost and methazolamide.

According to another aspect of the invention, there is provided a process for the preparation of a fixed dose pharmaceutical composition of the invention, wherein the process comprises mixing at least two anti-glaucoma agents with at least one or more pharmaceutically acceptable excipients; to provide the pharmaceutical composition.

According to yet another aspect of the present invention there is provided a method of treating glaucoma and/or reducing intraocular pressure comprising administering a fixed dose pharmaceutical composition according to the invention to a patient in need thereof.

According to another aspect of the invention, there is provided a fixed dose composition of the invention for use in medicine. Preferably, the use comprises treatment of glaucoma and/or in reducing of intraocular pressure.

According to another aspect of the invention, there is provided use of a pharmaceutical composition of the invention in the manufacture of a medicament for the treatment of glaucoma and/or the reduction of intraocular pressure.

DETAILED DESCRIPTION OF THE INVENTION:

The purpose of glaucoma therapy at the present time is to maintain the patient's visual function. Visual function damage severely impairs patients’ Quality of life (QOL). However, in providing treatment, one must not only bear in mind possible adverse effects and complications of the treatment, but also the social and economic burden imposed by hospital visits and/or hospitalization and the impairment to QOL caused by worry about blindness.
There are many anti-glaucoma drugs available, but the principle of drug treatment of the disease lies in obtaining the maximum effect with the minimum required drugs and the minimum adverse effects. For this reason, the mechanism of action, adverse effects, and contraindications of the drugs used must be understood. In addition, factors such as QOL, treatment costs, and compliance must also be taken into consideration.

As the therapeutic options in glaucoma include drug treatment, laser treatment, and surgical treatment, the appropriate therapeutic modality must be selected based on the individual patient and the disease stage and type. Concomitant use of multiple drugs may increase adverse effects and reduce compliance. Generally speaking, when three or more drugs are required to control IOP, other therapeutic options such as laser treatment or invasive surgery should be considered.

Glaucoma is a chronic, progressive disease, requiring long-term administration of eye drops and periodic follow up of the patient, and as there are no symptoms in many cases, it is essential to secure the patient's cooperation in order to achieve therapeutic success. Compliance in glaucoma drug treatment has been reported to be far worse than physicians believe. Non-compliance is an important factor in the progression of glaucomatous visual field damage. Therefore, compliance issues must be taken into account when the type of treatment is selected, and when visual field deterioration is observed, compliance issues must be verified before changing medications. Moreover, the improvement of compliance depends upon explanations of the disease, treatment, and adverse effects, keeping the treatment to a minimum, tailoring the treatment to the patient's lifestyle and providing proper administration guidance.

When monotherapy with glaucoma treatment agents does not produce a sufficient effect, these agents may be combined with other drugs. Although combinations of β-adrenergic blockers and sympathomimetics or combinations of prostaglandin analogues, which increase the uveoscleral outflow, and pilocarpine, which decreases uveoscleral outflow, appear to be unsuitable either from a pharmacological standpoint or from the standpoint of lowering IOP, these combinations frequently do reduce IOP in actual use. The combined effect of such administration has been confirmed in actual trial use.

Such combination therapy may involve different dosage regimens as well as different frequencies of administration of anti-glaucoma agents and thus it generally may result in non-
completion of therapy leading to the worsening of underlying disease as a result of such non-compliance, which is especially observed in patients.

Efforts to improve such compliance have been aimed at by simplifying the medication packaging, providing effective medication reminders, improving patient education, and limiting the number of medications prescribed simultaneously. However, such efforts have not been able to completely resolve the drawbacks associated with patient compliance.

The present invention provides a fixed dose pharmaceutical composition comprising anti-glaucoma agents which would ensure patient compliance due to simplification of therapy. As would be understood by a skilled person, the term "fixed dose composition" refers to a formulation comprising two or more active pharmaceutical ingredients combined in a single dosage form, wherein the composition comprises a combination of drugs present in a predetermined ratio. Anti-glaucoma agents for use in the present invention include, but are not limited to the combinations of tafluprost and dorzolamide, tafluprost and brinzolamide, tafluprost and acetazolamide, tafluprost and methazolamide.

The present invention thus provides a fixed dose pharmaceutical composition comprising a combination of tafluprost and dorzolamide, tafluprost and brinzolamide, tafluprost and acetazolamide, as well as tafluprost and methazolamide.

Potential advantages of such fixed dose combinations include an improvement of the benefit/risk assessment due to addition or potentiation of therapeutic activities of their substances, which results in a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination. Further, they are associated with a better safety profile or a level of efficacy above the one achievable by a single substance with an acceptable safety profile. Another advantage is the counteracting by one substance of an adverse reaction produced by another one.

It will be understood, however, that specific dose level and frequency of dosage of the combination according to the invention for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health,
sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The term "Tafluprost" is used in broad sense to include not only "Tafluprost" per se but also its pharmaceutically acceptable derivatives thereof. Suitable derivatives include pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable anhydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable esters, pharmaceutically acceptable isomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable tautomers, pharmaceutically acceptable complexes etc.

The term "Dorzolamide" is used in broad sense to include not only "Dorzolamide" per se but also its pharmaceutically acceptable derivatives thereof. Suitable derivatives include pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable anhydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable esters, pharmaceutically acceptable isomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable tautomers, pharmaceutically acceptable complexes etc. The dorzolamide can be present in compositions of the invention in the form of a free base or a salt. An example of such a salt for use in the invention is dorzolamide hydrochloride.

The term "Brinzolamide" is used in broad sense to include not only "Brinzolamide" per se but also its pharmaceutically acceptable derivatives thereof. Suitable derivatives include pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable anhydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable esters, pharmaceutically acceptable isomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable tautomers, pharmaceutically acceptable complexes etc. The brinzolamide can be present in compositions of the invention in the form of a free base or a salt.

The term "Acetazolamide" is used in broad sense to include not only "Acetazolamide" per se but also its pharmaceutically acceptable derivatives thereof. Suitable derivatives include pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically
acceptable hydrates, pharmaceutically acceptable anhydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable esters, pharmaceutically acceptable isomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable tautomers, pharmaceutically acceptable complexes etc.

The term "Methazolamide" is used in broad sense to include not only "Methazolamide" per se but also its pharmaceutically acceptable derivatives thereof. Suitable derivatives include pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable anhydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable esters, pharmaceutically acceptable isomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable tautomers, pharmaceutically acceptable complexes etc. The term "pharmaceutical composition" includes ocular dosage forms (solutions, suspensions, sol to gel systems, sprays, drops, liquid dispersions, suspensions, solutions, emulsions, gels, ointments, lotions, creams, ocular inserts, contact lenses, corneal shield, artificial tear inserts, subconjunctival inserts, filter paper strips, punctal plugs, liposomal preparations, injections, implants, depots) tablets, capsules (filled with powders, powders for reconstitution, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, multi unit pellet systems (MUPS), disintegrating tablets, dispersible tablets, granules, and microspheres, multiparticulates), sachets (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, multi unit pellet systems (MUPS), disintegrating tablets, dispersible tablets, granules, and microspheres, multiparticulates) and sprinkles and the like, however, other dosage forms such as liquid dosage forms (liquids, liquid dispersions, suspensions, solutions, emulsions, sprays, spot-on), liposomal formulations, injection preparations, implants, depots, gels, aerosols, ointments, creams, controlled release formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations etc may also be envisaged under the ambit of the invention.

Suitably, the fixed dose pharmaceutical composition, according to the present invention are presented in an ocular dosage forms such as but not limited to solutions, suspensions, sol to gel systems, liposomal preparations, hydrogels, sprays, drops, liquid dispersions, suspensions, nanosuspensions, emulsions, microemulsions, gels, in situ gels, ointments, creams, ocular
inserts, contact lenses, corneal shield, artificial tear inserts, subconjunctival inserts, colloidal drug delivery systems, nanoparticulates, microparticulates, niosomes, dendrimers, cyclodextrins, hydrogel systems, injections, implants, depots, punctual plugs, filter paper strips and the like.

Preferably, the fixed dose pharmaceutical composition comprises tafluprost in an amount of from about 0.00005 to about 0.05% w/v.

Preferably, the fixed dose pharmaceutical composition comprises dorzolamide in an amount of from about 0.1 to about 15% w/v.

Preferably, the fixed dose pharmaceutical composition comprising brinzolamide in an amount of from about 0.1 to about 15% w/v.

Preferably, the fixed dose pharmaceutical composition comprises acetazolamide in an amount of from about 0.1 to about 15% w/v.

Preferably, the fixed dose pharmaceutical composition comprises methazolamide in an amount of from about 0.1 to about 15% w/v.

Preferably, the fixed dose pharmaceutical composition comprises tafluprost in an amount of from about 0.00005 to about 0.05% w/v and dorzolamide in an amount of from about 0.1 to about 15% w/v.

Preferably, the fixed dose pharmaceutical composition comprises tafluprost in an amount of from about 0.00005 to about 0.05% w/v and brinzolamide in an amount of from about 0.1 to about 15% w/v.

Preferably, the fixed dose pharmaceutical composition comprises tafluprost in an amount of from about 0.00005 to 0.05% w/v and acetazolamide in an amount of from about 0.1 to about 15% w/v.

Preferably, the fixed dose pharmaceutical composition comprises tafluprost in an amount of from about 0.00005 to 0.05% w/v and methazolamide in an amount of from about 0.1 to about 15% w/v.
Further, the fixed dose pharmaceutical composition, according to the present invention, may be administered once daily, twice daily or thrice daily.

The inventors of the present invention have further observed that the solubility properties of anti-glucoma agents were improved by nanosizing leading to better bioavailability of the drug.

Nanonization of hydrophobic or poorly water-soluble drugs generally involves the production of drug nanocrystals through either chemical precipitation (bottom-up technology) or disintegration (top-down technology). Different methods may be utilized to reduce the particle size of the hydrophobic or poorly water soluble drugs. [Huabing Chen et al., discusses the various methods to develop nanoformulations in "Nanonization strategies for poorly water-soluble drugs," Drug Discovery Today, Volume 00, Number 00, March 2010].

The present invention thus provides a fixed dose pharmaceutical composition comprising tafluprost and dorzolamide, tafluprost and brinzolamide, tafluprost and acetazolamide, tafluprost and methazolamide wherein tafluprost, dorzolamide, brinzolamide acetazolamide and methazolamide are in the nanosize range.

The term "nanosize" as used herein refers to tafluprost, dorzolamide, brinzolamide acetazolamide and methazolamide particles having an average particle size of less than or equal to about 3000 nm.

The term "particles" as used herein refers to particles of tafluprost or dorzolamide, tafluprost or brinzolamide, tafluprost or acetazolamide, tafluprost or methazolamide.

The nanoparticles of the present invention can be obtained by any of the process such as but not limited to milling, precipitation, homogenization, high pressure homogenization, spray-freeze drying, supercritical fluid technology, emulsion/solvent evaporation, PRINT, thermal condensation, ultrasonication and spray drying.

The inventors of the present invention have also observed that the solubility properties of anti-glaucoma agents were improved by forming complexes with suitable complexing agents. Cyclodextrins are one such water-soluble complexing agents that are able to solubilize poorly soluble lipophilic drugs, and enhance their permeation through biological membranes, through
formation of water-soluble complexes. Accordingly, the fixed dose compositions of the present invention may comprise one or more cyclodextrins.

Suitable excipients may be used for formulating the various dosage forms according to the present invention. The composition of the invention may include excipients such as, but not limited to, vehicle, surfactant, antioxidants, polymers, stability enhancing agents, solubilizers, viscosity enhancing agents or suspending agents, lipids, isotonic agents, pH adjusting agent, preservatives, chelating agents, mucoadhesive agents, polyethoxylated castor oils and/or any combination thereof.

Surfactants are added in order to prevent the concentration of the prostaglandin derivatives from being lowered by improving water-solubility of the prostaglandin derivatives in the ophthalmic solution and by inhibiting the adsorption to the resinous container. Suitable amphoteric, non-ionic, cationic or anionic surfactants may be included in the fixed dose pharmaceutical composition of the present invention.

Surfactants for use in the present invention may comprise of one or more, but not limited to Polysorbates such as polyoxyethylene fatty esters such as polysorbate 80 [poly(oxyethylene)sorbitan monooleate], polysorbate 60 [poly(oxyethylene)sorbitan monostearate], polysorbate 40 [poly(oxyethylene)sorbitan monopalmitate], poly(oxyethylene)sorbitan monolaurate, poly(oxyethylene)sorbitan trioleate and polysorbate 65 [poly(oxyethylene)sorbitan tristearate], polyoxyethylene hydrogenated castor oils such as Cremophor RH 40 (PEG-40 Hydrogenated Castor Oil), Cremophor EL, polyoxyethylene hydrogenated castor oil 10, polyoxyethylene hydrogenated castor oil 40, polyoxyethylene hydrogenated castor oil 50 and polyoxyethylene hydrogenated castor oil 60, polyoxyethylene polyoxypropylene glycols such as polyoxyethylene (160) polyoxypropylene (30) glycol [Pluronic F68], polyoxyethylene (42) polyoxypropylene (67) glycol [Pluronic P123], polyoxyethylene (54) polyoxypropylene (39) glycol [Pluronic P85], polyoxyethylene (196) polyoxypropylene (67) glycol [Pluronic F127] and polyoxyethylene (20) polyoxypropylene (20) glycol [Pluronic L-44], polyoxyxyl 40 stearate and sucrose fatty esters, Sodium dodecyl sulfate (sodium lauryl sulfate), Lauryl dimethyl amine oxide, Tyloxapol, Docusate sodium, Cetyl trimethyl ammonium bromide (CTAB), Polyethoxylated alcohols, Polyoxylethylene sorbitan, Octoxynol, N, N-dimethyldecylamine-N-oxide, Hexadecyltrimethylammonium bromide,
Polyoxyl 10 lauryl ether, Brij, Bile salts (sodium deoxycholate, sodium cholate), Polyoxyl castor oil, Nonylphenol ethoxylate Cyclodextrins, Lecithin, Methylbenzethonium chloride. Carboxylates, Sulphonates, Petroleum sulphonates, alkylbenzenesulphonates, Naphthalenesulphonates, Olefin sulphonates, Alkyl sulphates, Sulphates, Sulphated natural oils and fats, Sulphated esters, Sulphated alkanolamides, Alkylphenols, ethoxylated and sulphated, Ethoxylated aliphatic alcohol, polyoxyethylene surfactants, carboxylic esters Polyethylene glycol esters, tocopherol polyethylene glycol succinate (TPGS), Anhydrosorbitol ester and it's ethoxylated derivatives, Glycol esters of fatty acids, Carboxylic amides, Monoalkanolamine condensates, Polyoxyethylene fatty acid amides, Quaternary amonium salts, Amines with amide linkages, Polyoxyethylene alkyl and alicyclic amines, N,N,N,N tetrasubstituted ethylenediamines 2- alkyl 1- hydroxyethyl 2-imidazolines, N -coco 3-aminopropionic acid/ sodium salt, N-tallow 3 -iminodipropionate disodium salt, N-carboxymethyl n dimethyl n-9 octadecenyl ammonium hydroxide, n-cocoamidethyl n-hydroxyethylglycine sodium salt and the like or combinations thereof.

Preferably, the surfactant is present in an amount from about 0.5% w/v or less.

Antioxidants are added in order to prevent the concentration of the prostaglandin derivatives from being lowered by inhibiting decomposition of the prostaglandin derivatives in the ophthalmic solution. Specific examples of antioxidants such as, but not limited to, sodium nitrite, ascorbic acid, L-ascorbic acid stearate, sodium hydrogensulfite, alphathioglycerin, ethylenediaminetetraacetic acid, erythorbic acid, cysteine hydrochloride, citric acid, tocopherol acetate, potassium dichloroisocyanurate, dibutylhydroxytoluene, 2,6-di-t-butyl-4-methylphenol, soybean lecithin, sodium thioglycollate, sodium thiomalate, natural vitamin E esters of vitamin E, tocopherol, ascorbyl pasthyminate, sodium pyrosulfite, butylhydroxyanisole, 1,3-butylene glycol, pentaerythyl tetrakis[3-(3,5-di-t-butyl-4-hydroxyphenyl)]propionate, propyl gallate, 2- mercaptobenzimidazole and oxyquinoline sulfate, ascorbate, mannitol, reduced glutathione, various carotenoids, cysteine, uric acid, taurine, tyrosine, superoxide dismutase, lutein, zeaxanthin, cryptoxanthin, astazanthin, iycopene, N-acetyl- cysteine, carnosine, gamma glutamylcysteine, quercitin, lactoferrin, dihydroliopoic acid, citrate, Ginkgo Biloba extract, tea catechins, bilberry extract, or, retinyl palmitate, derivatives and the like or combinations thereof.

Preferably, the antioxidant is present in an amount from about 0.00005% w/v to about 0.5% w/v.
Viscosity enhancing agents and/or suspending agents may be employed to thicken the tear film and increase corneal contact time, i.e., reduce the rate of tear fluid drainage. Such agents may include, but are not limited to, cellulose derivatives, methylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone and polyvinyl alcohol, Carbomer 974 P, carboxy methyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol (PVA), carbopol, carbophil, cross-linked carboxyl-containing polymers, ethyl cellulose, acacia, agar, alginic acid, sodium alginate, bentonite, carrageenan, gelatin, tragacanth, xanthan gum, gellan gum, pectin, poloxamer, xylol glucan, Smart Hydrogel™, polymethacrylic acid - polyethylene glycol and combinations thereof.

Preferably, the viscosity-enhancing and/or suspending agents are present in an amount from about 0.005% w/v to about 2% w/v.

Mucoadhesive agents may also be incorporated in the fixed dose pharmaceutical compositions of the present invention, which may include, but are not limited to, Poly (acrylic acid), carbomer, hyaluronan, chitosan, sodium carboxymethylcellulose, poly(galactouronic acid), sodium alginate, pectin, xanthan gum, xyloglucan gum, scleroglucan, hydroxypropylmethylcellulose, methylcellulose, poly(vinyl alcohol), poly(vinyl pyrrolidone) and combinations thereof.

Prostaglandin esters such as tafluprost are difficult to formulate in storage-stable solutions as they tend to be hydrolytically unstable. The fixed dose pharmaceutical compositions of the present invention, however, are storage stable. These compositions contain a stability-enhancing amount of a polyethoxylated castor oil, phosphonates, disodium edetate; sodium thiosulfate; and sodium stannate.

The polyethoxylated castor oils comprise, but are not limited to, PEG-2 to PEG-200 castor oils, as well as PEG-5 to PEG-200 hydrogenated castor oils or combinations thereof.

Preferably, the one or more polyethoxylated castor oils are present in an amount from about 0.02 and to about 20.0 % w/v.

Suitable lipids which may be used for liposomal preparations may comprise or constitute phospholipids or phospholipid derivatives or natural phospholipids and the like. The lipids may comprise a group selected from lecithins, pegylated lipids, phosphatidylglycerol (PG),
phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylcholine (PC), phosphatidylinositol (PI), phosphatidic acid (PA), DPG (bisphosphatidyl glycerol), PEOH (phosphatidyl alcohol) and cholesterol. Phospholipids for pH sensitive liposomes such as DSPE-PG8MG/ DSPE-PG8CH and the like.

Suitable solubilizers may also be incorporated in the fixed dose pharmaceutical compositions of the present invention, which may include, but are not limited to, polysorbate 80, polyoxyethylene hydrogenated castor oil 60, macrogal 4000, tyloxapol, fatty acid glycerol polyethylene glycol esters, fatty acid polyethylene glycol esters, polyethylene glycols, glycerol ethers, Cremophor EL or Cremophor RH 40® and the like or combinations thereof.

Various additives can be added such as tonicity adjusting agents or isotonic agents include, but are not limited to, sodium chloride, potassium chloride, dextrose, mannitol, calcium chloride, glycerine/glycerol or propylene glycol and the like and combinations thereof; buffering agents or pH adjusting agent include, but are not limited to, acetic acid or salts thereof, boric acid or salts thereof, phosphoric acid or salts thereof; citric acid or salts thereof, tartaric acid or salts thereof, hydrochloric acid, sodium hydroxide, potassium hydroxide, sodium dihydrogen phosphate dihydrate, sodium carbonate, sodium hydrogen carbonate, trometamol, disodium hydrogen phosphate or epsilon -aminocaproic acid, tromethamine and the like and combinations thereof; preservatives include, but are not limited to, soft preservatives, benzalkonium chloride, benzylammonium chloride, cetylethyl ammonium bromide, cetlypyridinium chloride, chlorhexidine gluconate, chlorhexidine acetate, chlorobutanol, benzethonium chloride, sorbic acid, potassium sorbate, polyaminopropyl biguanide, organic mercurials such as phenylmercuric acetate, phenylmercuric nitrate and thimerosal; Polyquad (Polyquaternium-1), thiomersal, chlorobutanol, phenyl mercuric nitrate, phenyl mercuric acetate, benzododecinium bromide (BDD), cetrimonium chloride, methyl parahydroxybenzoate, Polyquaternium ammonium chloride, hydrogen peroxide, phenyl ethyl alcohol, chlororesol parabens such as methyl and propyl paraben; hydroxy benzoates, methyl paraoxybenzoate, propyl paraoxybenzoate, ethyl paraoxybenzoate or butyl paraoxybenzoate; acids and their pharmaceutically acceptable salts such as sorbic acid, potassium sorbate, boric acid, borax, salicylic acid; Substituted alcohols and phenols such as chlorobutanol, benzyl alcohol; phenyl ethanol, betaphenylethyl alcohol, phenylethyl alcohol, phenoxyethanol; Amides such as acetamide; stabilized oxychloro complex
(SOC), sofzia, and sodium perborate and the like or combinations thereof; chelating agents such as, but are not limited to, edetic acid (EDTA) or one of the known salts thereof, e.g. sodium EDTA or disodium EDTA dihydrate (sodium edetate), trisodium edetate, malic acid, sodium citrate, condensed sodium phosphate in the concentrations.

Optionally, the fixed dose pharmaceutical compositions of the present invention may be preservative free.

Further, the fixed dose pharmaceutical compositions of the present invention may be heat stable.

Further, the storage temperature for an ophthalmic formulation may sometimes increase during distribution or storage. In the case where a thermally unstable drug is present in the ophthalmic formulation, a rise of the storage temperature, causes a decrease in the desired drug efficacy or discoloration and formation of suspended matter.

The inventors of the present invention, in order to prevent the degradation of a thermally unstable drug, have formulated heat stable fixed dose pharmaceutical compositions.

The fixed dose pharmaceutical compositions of the present invention have a pH of about 3 to 8, preferably from about 4 to 7 and an osmolality between 260 to 320 milliOsmoles per kilogram (mOsm/kg).

The fixed dose pharmaceutical compositions may further comprise sterile water for injection as a vehicle. Other aqueous and non-aqueous vehicles may also be used as a vehicle.

The fixed dose pharmaceutical compositions of the present invention can be packed in a resinous container of material such as, but not limited to, polyethylene, polypropylene, polyethylene terephthalate, polyvinyl chloride, acrylic resins, polystyrene, polymethyl methacrylate and nylon. These resins can be high-density resins or low-density resins.

Preferably, the fixed dose pharmaceutical compositions are packaged in a "small volume" container. As used herein, the term "small volume" container shall mean a container of a size sufficient to hold a quantity of the fixed dose pharmaceutical composition sufficient for 1 - 3 doses per day over 1 - 2 months, generally about 20 mL or less. For example, small volume containers include 5 mL, 10 mL and 15 mL sized bottles.
Small volume bottles made from syndiotactic polypropylene are easier to squeeze than those made from isotactic polypropylene, and oval bottles are easier to squeeze than round bottles. Accordingly, the aqueous compositions adapted for topical ophthalmic administration are preferably packaged in oval, syndiotactic polypropylene bottles.

Further, the fixed dose pharmaceutical compositions of the present invention may be dispensed in a unit dose container or a multi dose container.

The pharmaceutical compositions may also be administered in the form of punctual plugs made of silicone, collagen and the like, implants, inserts would also be preferred as per need.

There is also provided a process for preparing the fixed dose pharmaceutical composition of the present invention, which process comprises (a) adding the active agents to the vehicle and optionally other excipients (b) making up the volume with vehicle followed by aseptic filtration.

The present invention also provides a method of reducing intra ocular pressure by administering a fixed dose pharmaceutical composition comprising tafluprost and dorzolamide, tafluprost and brinzolamide, tafluprost and acetazolamide, tafluprost and methazolamide.

The present invention also provides the use of treating glaucoma by administering a fixed dose pharmaceutical composition comprising tafluprost and dorzolamide, tafluprost and brinzolamide, tafluprost and acetazolamide, tafluprost and methazolamide.

The fixed dose pharmaceutical composition of the present invention, may further comprise at least one additional preventive or therapeutic drug for glaucoma or ocular hypertension, wherein the other preventive or therapeutic classes of drugs for glaucoma or ocular hypertension is selected from, but are not limited to, nonselective sympathomimetic drug, an a2-receptor agonist, an a1-receptor antagonist, a β-receptor antagonist, a parasympathomimetic drug and a Rho-kinase inhibitor. Suitably, the nonselective sympathomimetic drugs include dipivefrin, a2-receptor agonist agents includes brimonidine or apraclonidine, a1-receptor antagonist agent includes bunazosin, β-receptor antagonist includes timolol, befunolol, carteolol, nipradilol, betaxolol, levobunolol or metipranolol, parasympathomimetic drug includes pilocarpine.

The following examples is for the purpose of illustration of the invention only and is not intended in any way to limit the scope of the present invention.
Example 1:

Tafluprost and Dorzolamide Hydrochloride Ophthalmic Solution (Unit Dose)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Quantity (%w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tafluprost</td>
<td>0.0015</td>
</tr>
<tr>
<td>2</td>
<td>Dorzolamide Hydrochloride</td>
<td>2.23</td>
</tr>
<tr>
<td>3</td>
<td>Glycerol</td>
<td>2.25</td>
</tr>
<tr>
<td>4</td>
<td>Polysorbate 80</td>
<td>0.075</td>
</tr>
<tr>
<td>5</td>
<td>Disodium edetate</td>
<td>0.05</td>
</tr>
<tr>
<td>6</td>
<td>Sodium dihydrogen phosphate dihydrate</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>Sodium hydroxide/ Hydrochloric acid</td>
<td>q.s. to pH 5.5-5.7</td>
</tr>
<tr>
<td>8</td>
<td>Water for Injection</td>
<td>q.s. to 100 ml</td>
</tr>
</tbody>
</table>

Process:

1) Polysorbate 80, tafluprost was added in part quantity of water for injection.
2) Dorzolamide hydrochloride, disodium edetate, sodium dihydrogen phosphate dihydrate and glycerol was added in part quantity of water for injection and the pH was adjusted with NaOH/ HCl.
3) The solution obtained in step (1) was added to the solution obtained in step (2) and the final volume was made with water for injection and was aseptically filtered.

Example 2:

Tafluprost and Dorzolamide Hydrochloride Ophthalmic Solution (Multi Dose)
Tafluprost and Dorzolamide Ophthalmic Solution (Unit Dose)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Quantity (% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tafluprost</td>
<td>0.0015</td>
</tr>
<tr>
<td>2</td>
<td>Dorzolamide Hydrochloride</td>
<td>2.23</td>
</tr>
<tr>
<td>3</td>
<td>Glycerol</td>
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<td>Polysorbate 80</td>
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<td>5</td>
<td>Disodium edetate</td>
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</tr>
<tr>
<td>6</td>
<td>Sodium dihydrogen phosphate dihydrate</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>Sodium hydroxide/ Hydrochloric acid</td>
<td>q.s. to pH 5.5-5.7</td>
</tr>
<tr>
<td>8</td>
<td>Benzalkonium chloride</td>
<td>0.01</td>
</tr>
<tr>
<td>9</td>
<td>Water for Injection</td>
<td>q.s. to 100 ml</td>
</tr>
</tbody>
</table>

**Process:**

1) Polysorbate 80, tafluprost was added in part quantity of water for injection.

2) Dorzolamide hydrochloride, disodium edetate, sodium dihydrogen phosphate dihydrate, glycerol and benzalkonium chloride was added in part quantity of water for injection and the pH was adjusted with NaOH/HC1.

3) The solution obtained in step (1) was added to the solution obtained in step (2) and the final volume was made with water for injection and was aseptically filtered.

**Example 3:**

Tafluprost and Dorzolamide Ophthalmic Solution (Unit Dose)
Process:

1) Polysorbate 80, tafluprost was added in part quantity of water for injection.

2) Dorzolamide, disodium edetate, sodium dihydrogen phosphate dihydrate and glycerol was added in part quantity of water for injection and the pH was adjusted with NaOH/HCl.

3) The solution obtained in step (1) was added to the solution obtained in step (2) and the final volume was made with water for injection and was aseptically filtered.

Example 4:

Tafluprost and Dorzolamide Ophthalmic Solution (Multi Dose)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Quantity (%w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tafluprost</td>
<td>0.0015</td>
</tr>
<tr>
<td>2</td>
<td>Dorzolamide</td>
<td>2.00</td>
</tr>
<tr>
<td>3</td>
<td>Glycerol</td>
<td>2.25</td>
</tr>
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<td>4</td>
<td>Polysorbate 80</td>
<td>0.075</td>
</tr>
<tr>
<td>5</td>
<td>Disodium edetate</td>
<td>0.05</td>
</tr>
<tr>
<td>6</td>
<td>Sodium dihydrogen phosphate dihydrate</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>Sodium hydroxide/ Hydrochloric acid</td>
<td>q.s. to pH 5.5-5.7</td>
</tr>
<tr>
<td>8</td>
<td>Benzalkonium chloride</td>
<td>0.01</td>
</tr>
<tr>
<td>9</td>
<td>Water for Injection</td>
<td>q.s. to 100 ml</td>
</tr>
</tbody>
</table>

Process:

1) Polysorbate 80, tafluprost was added in part quantity of water for injection.
2) Dorzolamide, disodium edetate, sodium dihydrogen phosphate dihydrate, glycerol and benzalkonium chloride was added in part quantity of water for injection and the pH was adjusted with NaOH/ HCl.

3) The solution obtained in step (1) was added to the solution obtained in step (2) and the final volume was made with water for injection and was aseptically filtered.

Example 5

Tafluprost and Dorzolamide heat stable ophthalmic solution

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Quantity (%w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tafluprost</td>
<td>0.0015</td>
</tr>
<tr>
<td>2</td>
<td>Dorzolamide HCl</td>
<td>2.23</td>
</tr>
<tr>
<td>3</td>
<td>Glycerol</td>
<td>1.70</td>
</tr>
<tr>
<td>4</td>
<td>Polysorbate 80</td>
<td>0.075</td>
</tr>
<tr>
<td>5</td>
<td>Disodium edetate</td>
<td>0.05</td>
</tr>
<tr>
<td>6</td>
<td>Tromethamine</td>
<td>0.12</td>
</tr>
<tr>
<td>7</td>
<td>Benzalkonium chloride</td>
<td>0.01</td>
</tr>
<tr>
<td>8</td>
<td>Sodium hydroxide/ Hydrochloric acid</td>
<td>q.s. to pH 5.5-5.7</td>
</tr>
<tr>
<td>9</td>
<td>Water for Injection</td>
<td>q.s. to 100 ml</td>
</tr>
</tbody>
</table>

Process:

1) Polysorbate 80 and tafluprost was added and dissolved in part quantity of water for injection to obtain a solution.
2) Dorzolamide hydrochloride, disodium edetate, tromethamine, glycerol and benzalkonium chloride were added and dissolved in remaining quantity of water for injection and pH was adjusted with sodium hydroxide/hydrochloric acid to obtain a solution.

3) The solution obtained in step (1) was added to the solution obtained in step (2) and the volume was made up with water for injection and was aseptically filtered.

**Example 6:**

Tafluprost and Brinzolamide Ophthalmic Suspension

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Quantity (%w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tafluprost</td>
<td>0.0015</td>
</tr>
<tr>
<td>2</td>
<td>Brinzolamide</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>Carbomer 974 P</td>
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</tr>
<tr>
<td>4</td>
<td>Tyloxapol</td>
<td>0.025</td>
</tr>
<tr>
<td>5</td>
<td>Glycerol</td>
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</tr>
<tr>
<td>6</td>
<td>Polysorbate 80</td>
<td>0.075</td>
</tr>
<tr>
<td>7</td>
<td>Disodium edetate</td>
<td>0.05</td>
</tr>
<tr>
<td>8</td>
<td>Sodium dihydrogen phosphate dihydrate</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td>Sodium hydroxide/ Hydrochloric acid</td>
<td>q.s. to pH 5.5-6.7</td>
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<tr>
<td>10</td>
<td>Benzalkonium chloride</td>
<td>0.01</td>
</tr>
<tr>
<td>11</td>
<td>Water for Injection</td>
<td>q.s. to 100 ml</td>
</tr>
</tbody>
</table>

**Process:**

1) Polysorbate 80 and tafluprost was added in part quantity of water for injection.
2) Carbomer was added in another part quantity of water for injection
3) Disodium edetate, sodium dihydrogen phosphate dihydrate, glycerol and benzalkonium chloride was added in third part quantity of water for injection
4) The solution obtained in step (3) was added to step (2) and the pH was adjusted with NaOH/ HCl and was bulk sterilized.
5) The solution obtained in step (4) was cooled and the tafluprost solution obtained in step (1) was added to it.

6) Brinzolamide was aseptically added to tyloxapol and fourth part quantity of water for injection and was homogenized to obtain a slurry.

7) The slurry obtained in step (6) was milled and subjected to microfiltration.

8) The milled slurry obtained in step (7) was added to the solution obtained in step (5).

9) The final volume was made up with remaining quantity of water for injection.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise.
Claims

1. A fixed dose pharmaceutical composition comprising at least two anti-glaucoma agents and one or more pharmaceutically acceptable excipients.

2. The fixed dose pharmaceutical composition according to claim 1, wherein at least one or both anti-glaucoma agents are in the form of a pharmaceutically acceptable derivative thereof.

3. The fixed dose pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable derivative thereof is a salt, solvate, complex, hydrate, isomer, ester, tautomer, anhydrate, enantiomer, polymorph or prodrug.

4. The fixed dose pharmaceutical composition according to any preceding claim, wherein the anti-glaucoma agents comprise a carbonic anhydrase inhibitor.

5. The fixed dose pharmaceutical composition according to any preceding claim, wherein the anti-glaucoma agents comprise a prostaglandin derivative.

6. The fixed dose pharmaceutical composition according to any preceding claim, wherein the anti-glaucoma agents comprise a carbonic anhydrase inhibitor and a prostaglandin derivative.

7. The fixed dose pharmaceutical composition according to claim 5 or 6, wherein the prostaglandin derivative is tafluprost.

8. The fixed dose pharmaceutical composition according to any one of claims 4 to 7, wherein the carbonic anhydrase inhibitor is dorzolamide.

9. The fixed dose pharmaceutical composition according to any one of claims 4 to 7, wherein the carbonic anhydrase inhibitor is brinzolamide.

10. The fixed dose pharmaceutical composition according to any one of claim 4 to 7, wherein the carbonic anhydrase inhibitor is acetazolamide.

11. The fixed dose pharmaceutical composition according to any one of claim 4 to 7, wherein the carbonic anhydrase inhibitor is methazolamide.
12. The fixed dose pharmaceutical composition according to any preceding claim, wherein the composition is suitable for ocular administration.

13. The fixed dose pharmaceutical composition according to any preceding claim, wherein the composition for ocular administration is provided in the form of a solution, a suspension, a sol to gel system, a liposomal preparation, a hydrogel, a spray, a drop, a liquid dispersion, a nanosuspension, an emulsion, a microemulsion, a gel, a in situ gel, an ointment, a cream, an ocular insert, contact lenses, a corneal shield, an artificial tear insert, a subconjunctival insert, an injection, an implant, a depot, a punctual plug or a filter paper strip.

14. The fixed dose pharmaceutical composition according to any one of claims 7 to 13 wherein the tafluprost is present in the composition in an amount from about 0.00005% w/v to about 0.05% w/v.

15. The fixed dose pharmaceutical composition according to any one of claims 8 to 13, wherein the dorzolamide is present in an amount from about 0.1% w/v to about 15% w/v.

16. The fixed dose pharmaceutical composition according to any one of claims 9 to 13, wherein the brinzolamide is present in an amount from about 0.1% w/v to about 15% w/v.

17. The fixed dose pharmaceutical composition according to any one of claims 10 to 13, wherein the acetazolamide is present in an amount of from about 0.1% w/v to about 15% w/v.

18. The fixed dose pharmaceutical composition according to any one of claims 11 to 13, wherein the methazolamide is present in an amount of from about 0.1% w/v to about 15% w/v.

19. The fixed dose pharmaceutical composition according to any preceding claim, wherein the at least one or more pharmaceutically acceptable excipients comprise: vehicle, surfactant, antioxidants, polymers, stability enhancing agents, solubilizers, viscosity enhancing agents or suspending agents, lipids, isotonic agents, pH adjusting agent, preservatives, chelating agents, and/or any combination thereof.

20. The fixed dose pharmaceutical composition according to claim 19, wherein the excipients comprise an amphoteric, non-ionic, cationic or anionic surfactant or combinations thereof.
21. The fixed dose pharmaceutical composition according to claim 19 or 20, wherein the excipients comprise a viscosity enhancing or suspending agent.

22. The fixed dose pharmaceutical composition according to claim 19, 20 or 21, wherein the excipients comprise a solubilizer.

23. The fixed dose pharmaceutical composition according to any one of claims 19 to 22, wherein the excipients comprise a mucoadhesive agent.

24. The fixed dose pharmaceutical composition according to any preceding claim, wherein the pH of the composition is from about 3 to about 8.

25. A process for preparing the fixed dose pharmaceutical composition according to any preceding claim, wherein the process comprises mixing at least two anti-glaucoma agents with at least one pharmaceutically acceptable excipients; to provide the pharmaceutical composition.

26. The fixed dose pharmaceutical composition according to any one of claim 1 to 24, for use in medicine.

27. The fixed dose pharmaceutical composition for use according to claim 26, in the treatment of glaucoma and/or in reducing of intra ocular pressure.

28. The fixed dose composition according to claim 27, wherein the use comprises administering the pharmaceutical composition once daily, twice daily or thrice daily.

29. Use of the fixed dose pharmaceutical composition according to any of claims 1 to 24 in the manufacture of a medicament for the treatment of glaucoma and/or the reduction of intra ocular pressure.

30. A method of treating glaucoma and/or reducing intra ocular pressure comprising administering the fixed dose pharmaceutical composition according to any one of claims 1 to 24 to a patient in need thereof.

31. A method according to claim 30, wherein the method comprises administering the fixed dose pharmaceutical composition to a patient in need thereof, in an amount of once daily, twice daily, or thrice daily.
32. The fixed dose pharmaceutical composition as substantially described herein with reference to the examples.

33. The process of manufacturing a fixed dose pharmaceutical composition as substantially described herein with reference to the examples.
A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/382 A61K31/5575 A61P27/06
ADD.
According to International Patent Classification (IPC) and/or both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<td>1-8, 12-15, 19-33</td>
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</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier application or patent but published on or after the international filing date
- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O** document referring to an oral disclosure, use, exhibition or other means
- **P** document published prior to the international filing date but later than the priority date claimed

**T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

**S** document member of the same patent family

Date of the actual completion of the international search
12 August 2014

Date of mailing of the international search report
21/11/2014

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer
Uryga-Pol owy, V
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2.☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

    see additional sheet

1.☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2.☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3.☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4.☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

   8, 15 (completely) ; 1-7, 12-14, 19-33 (partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/21 0 (continuation of first sheet (2)) (April 2005)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 8, 15 (completely) ; 1-7, 12-14, 19-33 (partially)
   a fixed dose pharmaceutical composition comprising at least two anti-glaucoma agents and one or more pharmaceutically acceptable excipients, wherein the anti-glaucoma agents comprise dorzolamide

2. claims: 9, 16 (completely) ; 1-7, 12-14, 19-33 (partially)
   a fixed dose pharmaceutical composition comprising at least two anti-glaucoma agents and one or more pharmaceutically acceptable excipients, wherein the anti-glaucoma agents comprise brinzolamide

3. claims: 10, 17 (completely) ; 1-7, 12-14, 19-33 (partially)
   a fixed dose pharmaceutical composition comprising at least two anti-glaucoma agents and one or more pharmaceutically acceptable excipients, wherein the anti-glaucoma agents comprise acetazolamide

4. claims: 11, 18 (completely) ; 1-7, 12-14, 19-33 (partially)
   a fixed dose pharmaceutical composition comprising at least two anti-glaucoma agents and one or more pharmaceutically acceptable excipients, wherein the anti-glaucoma agents comprise methazolamide
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