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(54) **PHARMACEUTICAL COMPOSITIONS  
COMPRISING TIMOLOL**

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(57) **ABSTRACT**

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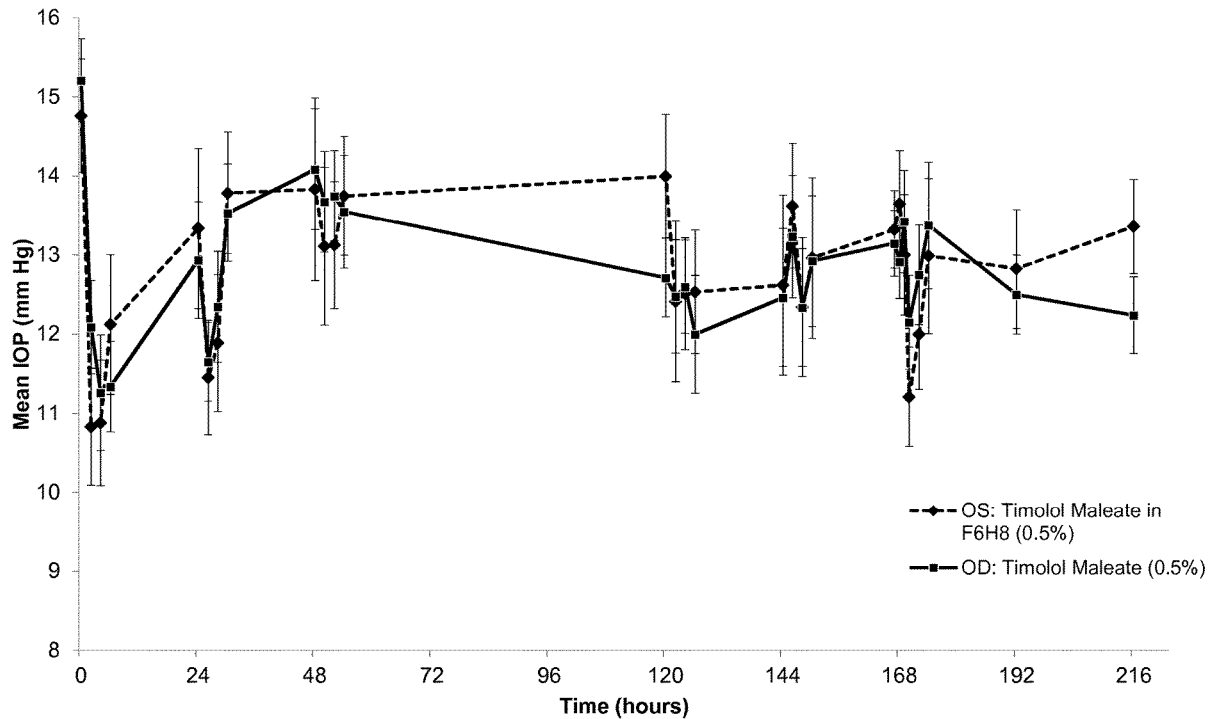
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The present invention relates to pharmaceutical composition comprising the beta 1( $\beta_1$ )-receptor blocker timolol and a liquid vehicle comprising a semifluorinated alkane. The pharmaceutical composition of the present invention may be useful for topical administration, for example ophthalmic topical administration and for use in the treatment of glaucoma, increased intraocular pressure, ocular hypertension and/or a symptom associated therewith.

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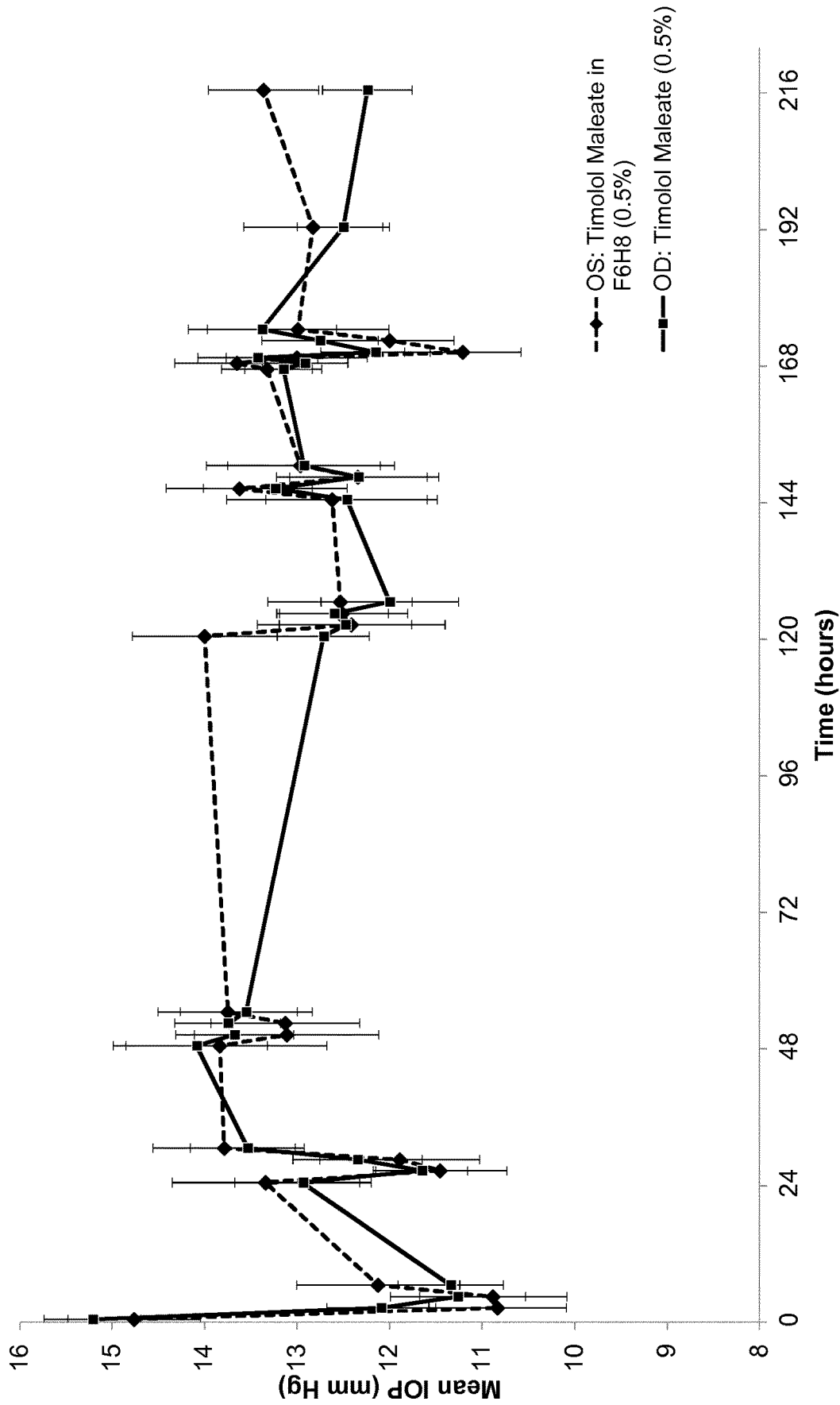


Figure 1

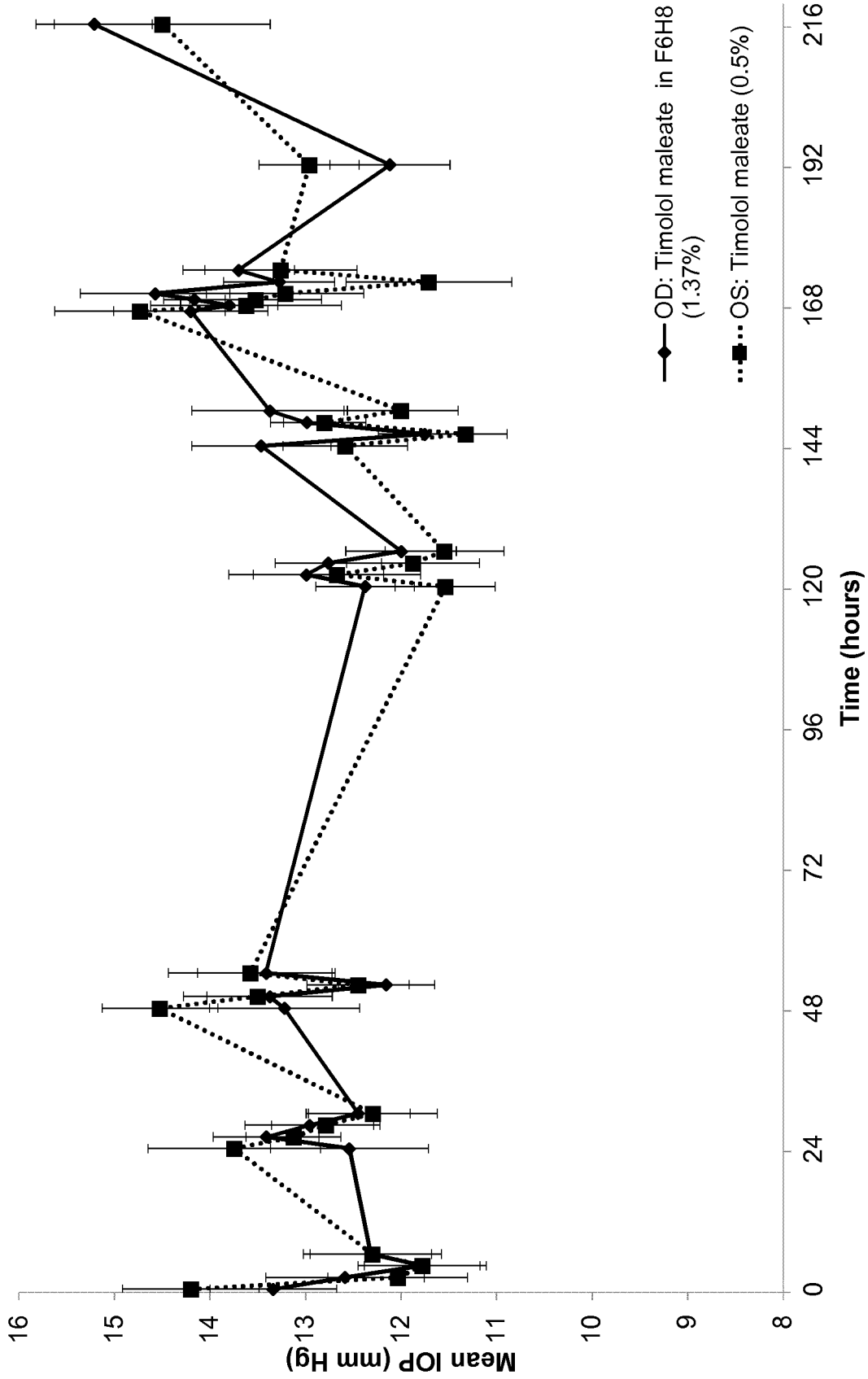


Figure 2

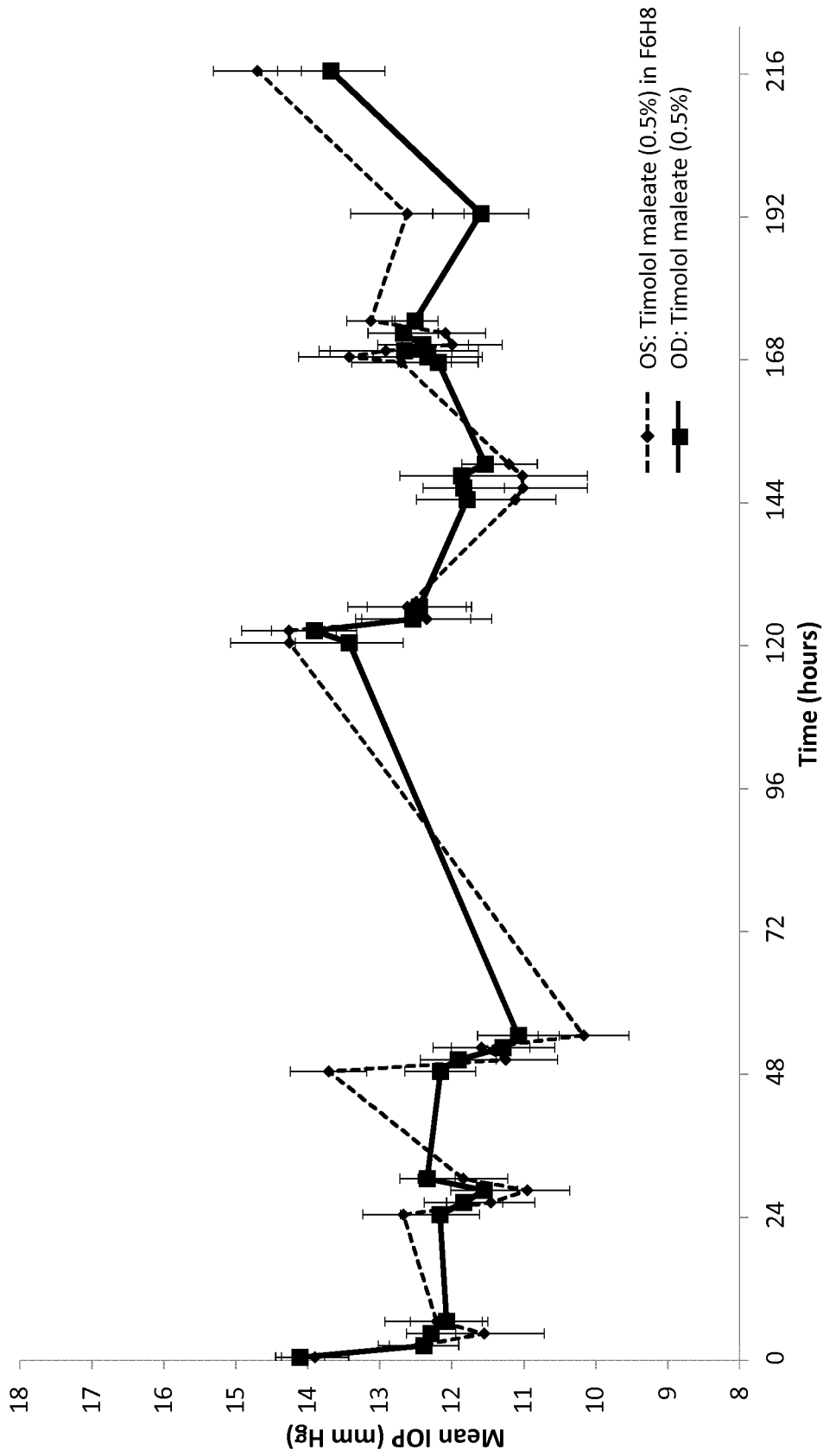


Figure 3

## PHARMACEUTICAL COMPOSITIONS COMPRISING TIMOLOL

### BACKGROUND

**[0001]** The present invention relates to a pharmaceutical composition comprising a) timolol and/or a pharmaceutically acceptable salt thereof and b) a liquid vehicle comprising a semifluorinated alkane. The pharmaceutical composition of the present invention may be useful for topical administration, especially ophthalmic topical administration.

**[0002]** Pharmaceutical compositions in liquid form represent one of the preferred types of drug formulations. Certain routes of topical administration, such as ophthalmic administration, typically require the liquid form in order to provide for an efficient delivery of the active ingredient and a patient-friendly mode of use.

**[0003]** The simplest type of liquid formulation is a solution, such as an aqueous solution of the active pharmaceutical ingredient. In certain cases, however, the development of a more complex formulation such as a suspension may be considered. For example, if a drug substance is very poorly soluble in aqueous or other biocompatible solvent systems, or if it is hydrolytically labile, a simple solution may not be feasible or represent the best choice.

**[0004]** Timolol belongs to a class of compounds named beta-blockers. Timolol in its oral form is used to treat high blood pressure and prevent heart attacks. In its ophthalmic form is used to treat open-angle glaucoma.

**[0005]** Beta-blockers act by blocking beta-receptors at the level of the ciliary body and by reducing the aqueous humour production, thereby reducing the intraocular pressure (IOP). Two types of topical beta-blockers are available for use in the treatment of glaucoma: non-selective beta-blockers, which block both beta 1 ( $\beta_1$ )- and beta 2 ( $\beta_2$ )-adrenoceptors; and cardio-selective beta blockers, which block only beta 1-receptors.

**[0006]** Timolol is a non-selective beta-adrenergic receptor antagonist. Timolol, when applied topically to the eye, has the action of reducing elevated, as well as normal, intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss and optic nerve damage.

**[0007]** Increased intraocular pressure is a frequent disorder of the eye which is often associated with optic nerve damage, in which case the disease is glaucoma. In the absence of optic nerve damage, the condition is referred to as ocular hypertension.

**[0008]** Normal intraocular pressure is usually defined as being in the range from 10 to 21 mmHg. The pressure results predominantly from the balance between the production rate and the drainage rate of the aqueous humour in the eye. In addition, it is influenced by the corneal thickness and rigidity. The intraocular pressure typically fluctuates around about 15 to 16 mmHg with amplitudes of up to 6 mmHg. For example, it usually decreases in the night due to a decreased production of aqueous humour. It also responds to various physiological factors such as exercise, heart rate, respiration, fluid intake, as well as certain types of systemic or topical drugs.

**[0009]** The aqueous humour is produced by the ciliary bodies of the eye, from where it flows into the posterior chamber. The composition of the aqueous humour is very

similar to that of blood plasma but differs from the latter by a lower protein content. Its main constituents are water (99%), electrolytes (inorganic ions to maintain the physiological pH), low amounts of albumin and  $\beta$ -globulins, ascorbate, glucose, lactate, and amino acids.

**[0010]** From the posterior chamber, the aqueous humour is distributed via the pupil of the iris into the anterior chamber of the eye. From here, it flows through the so-called trabecular meshwork, which is a spongy tissue area lined by trabeculocytes whose main function is to drain the humour into a set of tubes called Schlemm's canal, from where the humour enters the blood circulation. The humour flow from the trabecular meshwork into the Schlemm's canal occurs via two different routes: either directly via the aqueous vein to the episcleral vein, or indirectly via collector channels to the episcleral vein by intrascleral plexus. This trabecular outflow pathway accounts for the major fraction of drained aqueous humour. In addition, there exists a second major drainage pathway which is the uveoscleral outflow, which is relatively independent of the intraocular pressure and normally accounts for only 5 to 10% of the aqueous humour drainage in healthy humans.

**[0011]** Ophthalmic timolol is available in the market as a solution (liquid) and an extended-release (long-acting) gel-forming solution (liquid that thickens to a gel when instilled in the eye). Timolol eye drops are usually instilled once or twice a day, at evenly spaced intervals, until pressure in the eye is controlled (about 4 weeks). Then it may be instilled once a day. Timolol gel-forming solution is usually instilled once a day.

**[0012]** Timoptic® (timolol maleate ophthalmic solution) is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. Timoptic® is supplied as a sterile, isotonic, buffered aqueous solution of timolol maleate in two dosage strengths. Each mL of Timoptic® 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of Timoptic® 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate). As inactive ingredients, monobasic and dibasic sodium phosphate, sodium hydroxide, water for injection and benzalkonium chloride 0.01% as preservative are included.

**[0013]** The effects of timolol maleate on the intraocular pressure in patients with chronic open angle glaucoma compared to epinephrine or pilocarpine has been described in *Drugs* 1979 January; 17(1):38-55.

**[0014]** U.S. Pat. No. 6,335,335 B2 describes a method to promote penetration of a beta blocker into the eye and to improve the retention of the beta blocker in the ocular tissues by incorporating a C3-C7 fatty acid into an eye drop containing the beta blocker. Highly water soluble components find in the highly hydrophobic corneal epithelium a barrier to the penetration of the components into the eye. It is therefore necessary to instill the eye drop containing the components in high dose or many times, so that a sufficient amount of the components penetrates in the eye tissues for lowering an intraocular pressure. However, in order to separate from the systemic effect of the beta blocker, to get more effect on lowering intraocular pressure and to get the prolonged action of the beta blocker, it is preferable to promote penetration of the drugs into the eye and to prolong retention of the drug in the eye than to instill a high amount of the eye drop and instill many times.

**[0015]** It is an object of the present invention to provide a novel pharmaceutical formulation comprising timolol and/or

a pharmaceutically acceptable salt thereof, which can be useful as a medicament, particularly for topical applications. It is a further object of the present invention to find a treatment of increased intraocular pressure, e.g. in association with open-angle glaucoma or ocular hypertension, which overcomes at least one of the limitations or disadvantages associated with prior art formulations.

**[0016]** A further object of the present invention is to provide liquid formulations of timolol and/or a pharmaceutically acceptable salt thereof which is effective in decreasing intraocular pressure at reduced target dosage compared to commercial timolol solutions.

**[0017]** Further objects of the invention will become clear on the basis of the following description, examples, and patent claims.

#### SUMMARY OF THE INVENTION

**[0018]** In a first aspect, the present invention provides a pharmaceutical composition comprising:

**[0019]** (a) timolol and/or a pharmaceutically acceptable salt thereof, and

**[0020]** (b) a liquid vehicle comprising a semifluorinated alkane.

**[0021]** In a second aspect, the present invention provides the composition of the first aspect of the invention for use as medicament, more specifically for the treatment of glaucoma, increased intraocular pressure, ocular hypertension and/or a symptom associated therewith.

**[0022]** In a further aspect, the present invention provides a method for the treatment of glaucoma, increased intraocular pressure, ocular hypertension and/or a symptom associated therewith, comprising administering to the eye of a subject in need thereof a pharmaceutical composition according to the first aspect of the present invention.

**[0023]** In yet a further aspect, the present invention provides a kit comprising the pharmaceutical composition according to the first or second aspect of the invention and a container for holding the pharmaceutical composition.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0024]** FIG. 1 is a graphical representation of the results of the measurement of the in-vivo intraocular pressure study according to Example 2 below in which a suspension of timolol at a concentration of 0.5% (w/v) in 1-perfluorohexyl-octane (F6H8) is administered once a day.

**[0025]** FIG. 2 is a graphical representation of the results of the measurement of the in-vivo intraocular pressure study according to Example 2 below in which a suspension of timolol at a concentration of 1.37% (w/v) in 1-perfluorohexyl-octane (F6H8) is administered once a day.

**[0026]** FIG. 3 is a graphical representation of the results of the measurement of the in-vivo intraocular pressure study according to Example 2 below in which a suspension of timolol at a concentration of 0.5% (w/v) in 1-perfluorohexyl-octane (F6H8) is administered twice a day.

#### DETAILED DESCRIPTION OF THE INVENTION

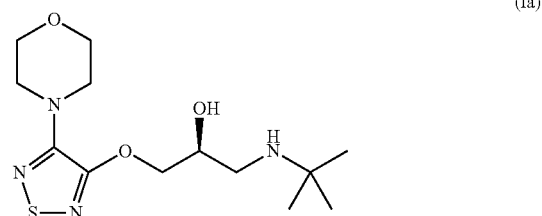
**[0027]** It has been found by the inventors that the composition of the invention surprisingly overcomes several drawbacks of previously known formulations of timolol.

In a first aspect, the present invention provides a pharmaceutical composition comprising:

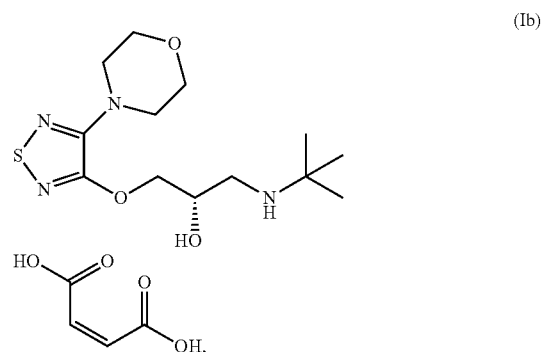
**[0028]** (a) timolol and/or a pharmaceutically acceptable salt thereof, and

**[0029]** (b) a liquid vehicle comprising a semifluorinated alkane.

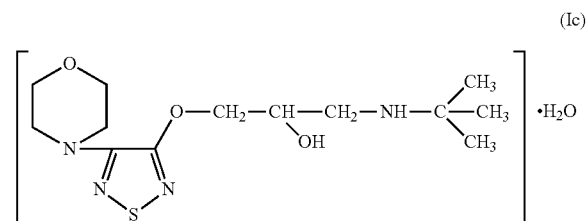
**[0030]** The pharmaceutical composition according to the present invention comprises as a first constituent (a) timolol and/or a pharmaceutically acceptable salt of timolol. The compound timolol, IUPAC name (2S)-1-(tert-butylamino)-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol, as used herein is of structural formula (a)



**[0031]** with the chemical formula  $C_{13}H_{24}N_4O_3S$  and molecular mass of 316.42 g/mol. Timolol is commercially available in form of its free base ((S)-timolol base) as described and shown by formula (Ia) above, as well as in the form of pharmaceutically acceptable salts such as, for example timolol maleate of formula (Ib), IUPAC name (2S)-1-(tert-butylamino)-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol maleate salt, molecular mass of 432.492 g/mol.



**[0032]** Timolol free base can also be provided in form of (S)-timolol base hemihydrate, as represented in formula (Ic) and having chemical formula  $C_{26}H_{50}N_8O_7S_2$  and molecular mass of 650.324 g/mol.



**[0033]** The pharmaceutical composition comprises timolol and/or a pharmaceutically acceptable salt of timolol, which means that the composition may comprise timolol in form of its free base as, for example shown in formula (Ia), either alone or in combination with one or a mixture of different pharmaceutically acceptable salts of timolol. Furthermore, the present pharmaceutical composition may comprise timolol in form of a salt, such as timolol maleate of formula (Ib) either alone or in form of a mixture with other pharmaceutically acceptable salts of timolol as described above.

**[0034]** In a preferred embodiment of the present invention, however, the pharmaceutical composition of the present invention comprises timolol in form of timolol maleate or (S)-timolol base hemihydrate. In another preferred embodiment, the pharmaceutical composition of the present invention comprises as component a) one selected from timolol maleate and (S)-timolol base hemihydrate. Preferably, the pharmaceutical composition of the present invention comprises as component a) timolol maleate. More preferably, the pharmaceutical composition of the present invention comprises as component a) the levo-isomer of timolol maleate.

**[0035]** Preferably, the timolol and/or another pharmaceutically acceptable salt of timolol as described above is present in the pharmaceutical composition according to present invention in a therapeutically effective amount. The term “a therapeutically effective amount” as used herein refers to a dose, concentration or strength which is useful for producing a desired pharmacological effect.

**[0036]** As a second constituent (b), the pharmaceutical composition according to the present invention comprises a liquid vehicle comprising a semifluorinated alkane. Some of the key advantages of the present invention are brought about by the presence of a semifluorinated alkane in the composition, functioning as a liquid vehicle for forming either a solution, dispersion or a suspension. The term ‘semifluorinated alkane’ as used herein means a compound in which a perfluorinated linear or branched, preferably linear hydrocarbon segment is attached to a linear or branched, preferably linear hydrocarbon segment.

**[0037]** In preferred embodiments, however, the pharmaceutical composition of the present invention or, more specifically, the liquid vehicle of the pharmaceutical composition of the present invention comprises a semifluorinated alkane of the general formula (II)



**[0038]** wherein the index n is an integer selected from 2 to 10, and m is an integer selected from 2 to 10. Preferably, the liquid vehicle of the pharmaceutical composition of the present invention comprises a semifluorinated alkane of the general formula (II) wherein the index n is an integer selected from 3 to 7, and m is an integer selected from 4 to 7, more preferably wherein the index n is an integer selected from 3 to 5, and m is an integer selected from 4 to 7.

**[0039]** Accordingly, said semifluorinated alkane as used in the composition of the present invention may preferably be selected from  $\text{CF}_3(\text{CF}_2)_3-(\text{CH}_2)_4\text{CH}_3$  (F4H5),  $\text{CF}_3(\text{CF}_2)_3-(\text{CH}_2)_5\text{CH}_3$  (F4H6),  $\text{CF}_3(\text{CF}_2)_3-(\text{CH}_2)_6\text{CH}_3$  (F4H7),  $\text{CF}_3(\text{CF}_2)_3-(\text{CH}_2)_7\text{CH}_3$  (F4H8),  $\text{CF}_3(\text{CF}_2)_4-(\text{CH}_2)_4\text{CH}_3$  (F5H5),  $\text{CF}_3(\text{CF}_2)_4-(\text{CH}_2)_5\text{CH}_3$  (F5H6),  $\text{CF}_3(\text{CF}_2)_4-(\text{CH}_2)_6\text{CH}_3$  (F5H7),  $\text{CF}_3(\text{CF}_2)_4-(\text{CH}_2)_7\text{CH}_3$  (F5H8),  $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_4\text{CH}_3$  (F6H5),  $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_5\text{CH}_3$  (F6H6),  $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_6\text{CH}_3$  (F6H7),  $\text{CF}_3(\text{CF}_2)_5-$

$(\text{CH}_2)_7\text{CH}_3$  (F6H8),  $\text{CF}_3(\text{CF}_2)_7-(\text{CH}_2)_7\text{CH}_3$  (F8H8). More preferably, said semifluorinated alkane may be selected from  $\text{CF}_3(\text{CF}_2)_3-(\text{CH}_2)_4\text{CH}_3$  (F4H5),  $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_5\text{CH}_3$  (F6H6),  $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_7\text{CH}_3$  (F6H8) and  $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_9\text{CH}_3$  (F6H10). Most preferably, said semifluorinated alkane may be selected from  $\text{CF}_3(\text{CF}_2)_3-(\text{CH}_2)_4\text{CH}_3$  (F4H5) and  $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_7\text{CH}_3$  (F6H8).

**[0040]** An alternative nomenclature for the specified semifluorinated alkanes as noted in parentheses below and as may be further used herein, is based on the general formula FnHm, wherein F means the linear perfluorinated hydrocarbon segment, H means the linear non-fluorinated hydrocarbon segment and n, m is the number of carbon atoms of the respective segment. For example, F4H5 may be used to denote 1-perfluorobutyl-pentane or  $\text{CF}_3(\text{CF}_2)_3-(\text{CH}_2)_4\text{CH}_3$  (which may be also, alternatively expressed as formula  $\text{F}(\text{CF}_2)_4(\text{CH}_2)_5\text{H}$ ), which has a linear perfluorinated segment F with four carbons (n=4) and a linear non-fluorinated hydrocarbon segment with five carbons (m=5). Furthermore, F6H8 may be used to denote 1-perfluorohexyl-octane or  $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_7\text{CH}_3$  (which may be also, alternatively expressed as formula  $\text{F}(\text{CF}_2)_6(\text{CH}_2)_8\text{H}$ ), which has a linear perfluorinated segment F with six carbons (n=6) and a linear non-fluorinated hydrocarbon segment with 8 carbons (m=8).

**[0041]** The pharmaceutical composition of the invention comprising of “a” semifluorinated alkane is to be understood herein, as comprising at least one semifluorinated alkane of Formula (II) as described above. Optionally, however, the composition may comprise of more than one, for example, a mixture of two or more semifluorinated alkanes of Formula (II), i.e. of any one of the semifluorinated alkane species as described above.

**[0042]** In a preferred embodiment, the pharmaceutical composition according to the present invention comprises a semifluorinated alkane of Formula (II) which is selected from 1-perfluorohexyl-octane ( $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_7\text{CH}_3$  (F6H8)) and 1-perfluorobutyl-pentane ( $\text{CF}_3(\text{CF}_2)_3-(\text{CH}_2)_4\text{CH}_3$  (F4H5)). In a particular preferred embodiment of the present invention, the semifluorinated alkane of Formula (II) is 1-perfluorohexyl-octane ( $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ , F6H8).

**[0043]** In yet a further embodiment, the liquid vehicle of the pharmaceutical composition of the present invention may consist of a semifluorinated alkane of Formula (II) as specified above. In this context also, the term “a” semifluorinated alkane is to be understood as at least one semifluorinated alkane, but may also include the option of more than one, or a plurality of semifluorinated alkane compounds. Accordingly, in one embodiment, the composition may consist of more than one semifluorinated alkane of Formula (II) as specified above.

**[0044]** In another embodiment, the pharmaceutical composition according to the present invention may comprise (a) timolol and/or a pharmaceutically acceptable salt thereof, and (b) a liquid vehicle comprising or essentially consisting of a semifluorinated alkane of general formula (II) as defined above, or a semifluorinated alkane selected from any one, or combination of the semifluorinated alkane compounds as defined above, and optionally, (c) one or more excipients.

**[0045]** As used herein, the term “consists” and related terms “consisting” or “consist” is to be understood as meaning that no other features, other than those prefaced by the term are present. In the context of compositions, if any other constituent or component is present in the composition other than those prefaced by such term, then it is present

only in trace or residual amounts such as to confer no technical advantage or relevance in respect of the object of the invention, such as may be further understood by the term ‘essentially’ or ‘substantially’ used in conjunction with these terms (e.g. ‘essentially consisting of’). It is to be understood that isomeric or olefinic impurities that originate from synthesis of semifluorinated alkanes and that are present in only trace or residual amounts, as these cannot be quantitatively removed upon purification, and that do not confer any technical advantage or relevance in respect of the object of the present invention, do fall under the above definition of such other constituent or component. In contrast, the term ‘comprising’ or related terms “comprises” or “comprise” in the context of the present compositions, is to be understood as meaning that other features, other than those prefaced by the term may be present in the composition.

**[0046]** In a further embodiment, the liquid vehicle of the present pharmaceutical composition as defined in any of the previous embodiments described above, preferably comprises a semifluorinated alkane or optionally, a mixture of semifluorinated alkanes in an amount of at least 70% (w/w), 75% (w/w), 85% (w/w), 90% (w/w), 95% (w/w), 98% (w/w), 98.5% (w/w), 99% (w/w), 99.5% (w/w), 99.8% (w/w) or at least 99.9% (w/w) of a semifluorinated alkane or a mixture of semifluorinated alkanes as described above, with respect to the total weight of the liquid vehicle. In a preferred embodiment, the liquid vehicle of the present pharmaceutical composition comprises a semifluorinated alkane in an amount of at least 98% w/w.

**[0047]** In a further embodiment, the liquid vehicle of the present invention essentially consists of 100% (w/w) of a semifluorinated alkane or mixture of semifluorinated alkanes.

**[0048]** The term “% (w/w)” as used herein and unless indicated otherwise refers to the amount of a component of a composition as a weight percentage in relation to the total weight of the liquid vehicle of the present pharmaceutical composition (with ‘w’ denoting weight).

**[0049]** In a particularly preferred embodiment, the liquid vehicle of the pharmaceutical composition according to the present invention comprises 1-perfluorohexyl-octane ( $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_7\text{CH}_3$  (F6H8)). In a further preferred embodiment, the liquid vehicle of the pharmaceutical composition of the present invention essentially consists of 1-perfluorohexyl-octane (F6H8). It is understood that a liquid vehicle essentially consisting of 1-perfluorohexyl-octane may comprise in trace or residual amounts isomeric or olefinic impurities (such as 2-perfluorohexyl-octane or 1-perfluorohexyl-octene) originating from synthesis of F6H8 which cannot be quantitatively removed upon purification.

**[0050]** In further preferred embodiments, the liquid vehicle of the pharmaceutical composition according to the present invention comprises 1-perfluorobutyl-pentane ( $\text{CF}_3(\text{CF}_2)_3-(\text{CH}_2)_4\text{CH}_3$  (F4H5)). In a further preferred embodiment, the liquid vehicle of the pharmaceutical composition of the present invention essentially consists of 1-perfluorobutyl-pentane (F4H5). It is understood that a liquid vehicle essentially consisting of 1-perfluorobutyl-pentane may comprise in trace or residual amounts isomeric or olefinic impurities (such as 2-perfluorobutyl-pentane or 1-perfluorobutyl-pentene) originating from synthesis of F4H5 which cannot be quantitatively removed upon purification.

**[0051]** The liquid semifluorinated alkanes as described above are chemically and physiologically inert, colourless and stable. Their typical densities range from 1.1 to 1.7  $\text{g/cm}^3$ , and their surface tension may be as low as 19  $\text{mN/m}$ . Semifluorinated alkanes of the RFRH type are insoluble in water but also somewhat amphiphilic, with increasing lipophilicity correlating with an increasing size of the non-fluorinated segment.

**[0052]** The liquid vehicle of the pharmaceutical composition comprising a semifluorinated alkane as described above may also comprise a further solubilizing agent, such as one or more solvents or co-solvents. In specific embodiments, the liquid vehicle of the present pharmaceutical composition may comprise a co-solvent, preferably an organic co-solvent.

**[0053]** As used herein, the term “solubilizing agent” may denote a compound or solvent or a co-solvent, preferably an organic solvent, that is miscible with the semifluorinated alkane or the mixture of different semifluorinated alkanes of the present liquid vehicle and that enhances or facilitates the solubility, or the dispersability of the active component timolol in the chosen liquid vehicle comprising a semifluorinated alkane as described above.

**[0054]** Examples of potentially useful organic co-solvents include glycerol, propylene glycol, polyethylene glycol, and ethanol. However, the concentration of the co-solvent should preferably be low relative to that of the semifluorinated alkane or semifluorinated alkane mixture. The co-solvent comprised in the liquid vehicle of the pharmaceutical composition according to the invention may be ethanol. If an organic co-solvent such as ethanol is used, it is recommendable to keep it at or below a level of approximately 10% (w/w) or 5% (w/w) or even 3% (w/w) with regard to the total weight of the liquid vehicle. Preferably, the content of ethanol is from about 0.1 to about 2% (w/w), and more preferably not more than about 1% (w/w) with regard to the total weight of the liquid vehicle. In some embodiments, the liquid vehicle of the present composition according to the invention, however, are free of an organic co-solvent.

**[0055]** In other embodiments, the solubilizing agent, that may be optionally comprised by the liquid vehicle of the present pharmaceutical composition, may preferably be present in an amount of up to 3% (w/w), or preferably of up to 2.5% (w/w) with respect to the total weight of the liquid vehicle. In a preferred embodiment, the liquid vehicle comprises a solubilising agent in amounts as low as up to 1% (w/w), preferably up to 0.5% (w/w) with respect to the total weight of the liquid vehicle. In another preferred embodiment, the liquid vehicle further comprises a solubilising agent in an amount of from about 2.5% to 0.5% (w/w), preferably of from about 1% to 0.5% (w/w) with respect to the weight of the liquid vehicle.

**[0056]** In some embodiments, the solubilizing agent may be a liquid excipient such as, for example, a further organic co-solvent as described above and/or an oil selected from glyceride oils, liquid waxes and liquid paraffin, or an organic solvent exhibiting a high degree of biocompatibility.

**[0057]** Examples of potentially useful liquid excipients comprise oily excipients which may be used in combination with one or more semifluorinated alkanes and include triglyceride oils, mineral oil, medium chain triglycerides (MCT), oily fatty acids isopropyl myristate, oily fatty alcohols, esters of sorbitol and fatty acids, oily sucrose esters or

any other substance which is physiologically tolerated by the eye. In one of the preferred embodiment, the liquid vehicle comprises a solubilizing agent in form of a liquid excipient. Further examples of potentially useful solubilizing agents as used herein are organic solvents. Preferred organic solvents include glycerol, propylene glycol, polyethylene glycol and ethanol. In yet further preferred embodiments, the liquid vehicle of the present pharmaceutical composition may comprise ethanol as the solubilizing agent, preferably in an amount of up to 1% (w/w), more preferably of up to 0.8% (w/w) and most preferred of up to 0.5% (w/w) with regard to the total weight of the liquid vehicle of the present pharmaceutical composition.

**[0058]** The pharmaceutical composition of the present invention comprises, as a constituent a), the active ingredient timolol and/or a pharmaceutically acceptable salt thereof, preferably timolol maleate, as described above. The present pharmaceutical composition may comprise timolol and/or a pharmaceutically acceptable salt thereof in an amount of from about 0.1% (w/v) to about 10% (w/v), or from about 0.1% (w/v) to about 5% (w/v), or from about 0.2% (w/v) to about 3% (w/v), or from about 0.2% (w/v) to about 2% (w/v), or from about 0.5% (w/v) to about 2% (w/v), or from about 0.5% (w/v) to about 1.5% (w/v).

**[0059]** In preferred embodiments, the present pharmaceutical composition comprises timolol and/or a pharmaceutically acceptable salt thereof, preferably timolol maleate or (S)-timolol hemihydrate, most preferably timolol maleate, in a concentration corresponding to a concentration of timolol free base of from about 0.5% (w/v) to about 2.0% (w/v), preferably from about 0.5% (w/v) to about 1.5% (w/v).

**[0060]** In a preferred embodiment, the pharmaceutical composition of the present invention comprises a) timolol maleate, preferably at a concentration of from about 0.4 to 3.4% (w/v), more preferably of from about 0.6 to about 3% (w/v), even more preferably of from about 0.68 to about 2.7% (w/v), most preferably at a concentration of from about 0.68% to about 2.1% (w/v).

**[0061]** Unless otherwise indicated, the term “% (w/v)” as used throughout herein in connection with the present pharmaceutical composition denotes the amount of a component of a composition as a weight percentage in relation to the total volume of the composition (with ‘w’ denoting the weight and ‘v’ denoting volume). For example, 0.05% (w/v) may be understood as relating to 0.5 mg of a component in 1 mL of the composition, and 0.1% (w/v) would correspond to 1.0 mg of a component in 1 mL of the composition.

**[0062]** The active component timolol and/or a pharmaceutically acceptable salt thereof, preferably timolol maleate or (S)-timolol hemihydrate, more preferably timolol maleate as described above, may be dissolved, dispersed or suspended in the liquid vehicle comprising a semifluorinated alkane as described below. Accordingly, the liquid pharmaceutical composition of the present invention may be in the form of a solution, preferably a clear solution or in form of a suspension.

**[0063]** In preferred embodiments, the pharmaceutical composition of the present invention is provided in form of a suspension. A suspension may be defined as a type of a dispersion, a dispersion being a system having at least one continuous (or coherent) phase and at least one discontinuous (or inner) phase which is dispersed in the continuous phase. In a suspension, the dispersed phase is in the solid state. Preferably, the suspensions useful for practising the

present invention are liquids, at least at physiological temperature, which means that the continuous phase is a liquid. Typically, the suspensions are also liquid at room temperature.

**[0064]** Preferably, the present invention provides a pharmaceutical composition in which particles of timolol and/or a pharmaceutically acceptable salt thereof, preferably timolol maleate or (S)-timolol hemihydrate, more preferably timolol maleate, as the dispersed phase are suspended in a liquid vehicle comprising a semifluorinated alkane, for example, a semifluorinated alkane of formula (II) as defined above as the continuous phase. Accordingly, in preferred embodiments of the present invention, the timolol and/or a pharmaceutically acceptable salt thereof is suspended in the liquid vehicle comprising a semifluorinated alkane.

**[0065]** In further preferred embodiment, the particles of timolol and/or a pharmaceutically acceptable salt thereof, preferably of timolol maleate or (S)-timolol hemihydrate, more preferably timolol maleate, are solid particles.

**[0066]** In further preferred embodiments, the pharmaceutical composition of the present invention comprises timolol and/or a pharmaceutically acceptable salt thereof suspended in the liquid vehicle b), at a concentration corresponding to a concentration of timolol free base of from 0.3 to 2.5% (w/v), preferably of from 0.5 to 2.0% (w/v), more preferably of from about 0.5 to 1.5% (w/v). For example, considering that 1.3668 mg timolol maleate correspond to 1.0 mg timolol free base, in a preferred embodiment of the present invention, component a) is timolol maleate suspended at a concentration of from about 0.4 to about 3.4% (w/v), preferably of from about 0.6 to about 3% (w/v), more preferably of from about 0.68 to about 2.7% (w/v), most preferably at a concentration of from about 0.68% to about 2.1% (w/v).

**[0067]** The particle size of the timolol and/or pharmaceutically acceptable salt thereof is preferably below about 100 m, which means that most of the particles, e.g. at least about 90% thereof, have a size below 100  $\mu\text{m}$ . Which type of particle diameter is considered as particle size will depend on the method used for particle size distribution, which in turn is selected to be appropriate for the type of solid material and the approximate size range. For example, laser diffraction or dynamic light scattering (also known as photon correlation spectroscopy or quasi-elastic light scattering) are appropriate methods for determining particle sizes in the colloidal and low micron range, whereas sedimentation analysis, sieve analysis or photoanalysis may be selected for larger particle sizes.

**[0068]** In a further preferred embodiment, at least about 90% of the suspended timolol and/or a pharmaceutically acceptable salt thereof have a particle size of not more than about 20  $\mu\text{m}$ , preferably of not more than about 15  $\mu\text{m}$ . In a most preferred embodiment, at least 90% of the suspended particles of timolol and/or a pharmaceutically acceptable salt thereof have a size lower than about 10  $\mu\text{m}$ , more preferred have size lower than about 5  $\mu\text{m}$ . Especially for ophthalmic administration, at least about 90% of the suspended particles of timolol and/or a pharmaceutically acceptable salt thereof have a size lower than about 20  $\mu\text{m}$ , preferably with at least about 90% of the suspended particles having a size of not more than about 15  $\mu\text{m}$ , more preferably of not more than about 10  $\mu\text{m}$ , most preferably of not more than about 5  $\mu\text{m}$ , as measured by state-of-the-art particle size distribution techniques (e.g. laser diffraction, dynamic light scattering).

**[0069]** The pharmaceutical composition comprising timolol and/or a pharmaceutically acceptable salt thereof, preferably timolol maleate, especially when suspended in a liquid vehicle comprising a semifluorinated alkane, displays advantageous stability, especially with regard to the size of the suspended particles. As known from other pharmaceutical compositions in form of suspensions, the suspended particles may aggregate, and depending on the forces by which the particles attract each other, the aggregates thus formed may be rather difficult to resuspend. A further problem associated with that is that in suspensions having non-uniform particle sizes there is a tendency for smaller particles to gradually dissolve, whereas larger particles grow through the deposition of dissolved material onto their surfaces (Ostwald ripening). In result, the particle size distribution of a suspension may become broader over time. Particles which grow beyond a certain size may be unsuitable for the intended use; for example, they may occlude an injection cannula or, in case of ophthalmic administration, irritate or even damage the ocular surface.

**[0070]** In contrast to this, it was found that the pharmaceutical composition of the present invention comprising timolol and/or a pharmaceutically acceptable salt thereof, especially when provided in form of a suspension, can be stored for prolonged periods of time without significantly changing their particle size distribution. Accordingly, the pharmaceutical composition of the present invention comprising timolol and/or a pharmaceutically acceptable salt thereof, preferably timolol maleate or (S)-timolol base hemihydrate, more preferably timolol maleate, in form of a suspension may be stored for extended periods of time, such as, for example for up to 1 year, or up to 6 months, or up to 3 months, or up to 2 months or up to 1 month without significantly changing their particle size distribution of the suspended particles. In exemplary embodiments, the present invention provides a pharmaceutical composition comprising timolol and/or a pharmaceutically acceptable salt thereof in form of a suspension, wherein at least about 90% of the suspended particles of timolol and/or a pharmaceutically acceptable salt thereof have a size of not more than about 15  $\mu\text{m}$ , after three weeks of storage at room temperature. The term room temperature as used herein is to be understood throughout as a temperature in the range of 20 to 25° C.

**[0071]** In another exemplary embodiment, the present invention provides a pharmaceutical composition comprising timolol and/or a pharmaceutically acceptable salt thereof in form of a suspension, wherein at least about 90% of the suspended particles of timolol and/or a pharmaceutically acceptable salt thereof have a size of not more than about 10  $\mu\text{m}$ , after three weeks of storage at room temperature.

**[0072]** In contrast to some other suspensions known in prior art, the pharmaceutical composition of the present invention when present in the form of a suspension usually requires no surfactant, or, if at all, only small amounts of surfactant, for its physical stabilisation. This is a significant advantage as surfactants have a substantial potential for irritation and local toxicity, especially when administered to the eye or by injection. According to one of the preferred embodiments, the pharmaceutical composition of the invention is substantially free of surfactant. In a further preferred embodiment, the total amount of surfactant or surfactants, if more than one surfactant is incorporated, is not more than about 5% (w/w), in particular not more than about 3% (w/w), or preferably not more than about 1% (w/w), respec-

tively, with regard to the total weight of the final composition. In further preferred embodiments, the amount is not more than about 0.5% (w/w), or not more than about 0.25% (w/w), respectively.

**[0073]** In this context, the semifluorinated alkanes as described herein, although they possess some amphiphilic properties due to their chemical structure which includes fluorinated and non-fluorinated alkyl (or alkylene) groups characterised by different degrees of lipophilicity, are not understood as being within the scope of surfactants.

**[0074]** The surfactants which may be absent or only present in small amounts include non-ionic, cationic, anionic, and zwitterionic surfactants as commonly used as excipients in various types of pharmaceutical compositions, e.g. as wetting agents, emulsifiers, dispersing agents, solubilisers and the like. Examples of surfactants which may be considered potentially useful include tyloxapol, poloxamers such as Pluronic F68LF or Lutrol F68, Pluronic L-G2LF and Pluronic L62D, polysorbates such as polysorbate 20 and polysorbate 80, polyoxyethylene castor oil derivatives, sorbitan esters, polyoxyl stearates, lecithins, purified or synthetic phospholipids, and mixtures of two or more thereof.

**[0075]** The pharmaceutical composition of the invention may further comprise excipients in range of up to about 10% (w/v), more preferably up to about 5% (w/v), even more preferably up to about 2% (w/v) such as, for example, non-fluorinated organic liquids, for example in order to modify the properties of the liquid vehicle, such as the viscosity. Such other liquid may be an oil selected from glyceride oils, liquid waxes, and liquid paraffin, or an organic solvent exhibiting a high degree of biocompatibility, or a mixture of more than one liquid excipients.

**[0076]** Examples of potentially useful oily excipients which may be used in combination with one or more semifluorinated alkanes as described above may include triglyceride oils (i.e. soybean oil, olive oil, sesame oil, cotton seed oil, castor oil, sweet almond oil), mineral oil (i.e. petrolatum and liquid paraffin), medium chain triglycerides (MCT), oily fatty acids, isopropyl myristate, oily fatty alcohols, esters of sorbitol and fatty acids, oily sucrose esters, or any other oily substance which is physiologically tolerated by the eye.

**[0077]** The composition of the present invention may, of course, comprise further pharmaceutical excipients as required or useful. Potentially useful excipients include acids, bases, antioxidants, stabilisers, synergists, colouring agents and thickening agents. In a preferred embodiment, however, the liquid vehicle of the pharmaceutical composition according to the present invention is free of any excipients.

**[0078]** Furthermore, the invention provides a means of formulating pharmaceutical compositions, preferably ophthalmic pharmaceutical compositions comprising timolol and/or a pharmaceutically acceptable salt thereof, preferably timolol maleate, which are microbiologically stable. This is due to the fact that semifluorinated alkanes as comprised by the liquid vehicle of the present compositions and as described above are not normally prone to microbial contamination. Hence, it is possible to formulate preservative-free ophthalmic compositions which are better tolerable for many patients, in particular patients suffering from an ophthalmic disease or condition. The preservative-free ophthalmic composition may be provided both in multi-dose or single-dose format.

**[0079]** Accordingly, although the pharmaceutical composition of the present invention may comprise a pharmaceutically acceptable preservative, in a preferred embodiment, the pharmaceutical composition of the present invention is free of a preservative. This is especially useful when the composition of the present invention is provided not only in dosage forms for single use (single dosage forms), but especially in multiple dosage forms with a plurality of doses.

**[0080]** In a further embodiment, water may also be present in the pharmaceutical composition of the present invention, however, preferably in small amounts of up to 1.0% (w/w) or even of only up to 0.1% (w/w) or less, based on the final composition (final dosage form). In a preferred embodiment, the pharmaceutical composition, preferably the liquid vehicle of the pharmaceutical composition of the present invention is essentially free of water, whereas the residual water may be attributed to the potential residual water content of the active ingredient timolol and/or a pharmaceutically acceptable salt thereof, especially timolol maleate. The term ‘essentially’ as used herein means if present then in trace or residual amounts such as to confer no technical advantage or relevance in respect of the object of the invention.

**[0081]** For example, 1-perfluorohexyl-octane (F6H8) or 1-perfluorobutyl-pentane (F4H5) as preferred semifluorinated alkanes in some embodiments of the present invention do not comprise any water, or have a water content of no more than the maximal solubility of water in 1-perfluorohexyl-octane or in 1-perfluorobutyl-pentane; for example 1-perfluorobutyl-pentane has a water-content of less than  $1.6 \times 10^{-4}$  mg/ml as determined by methods known in the art for moisture analysis, such as Karl-Fischer titration methods.

**[0082]** In preferred embodiments, the pharmaceutical composition of the present invention essentially consists of timolol maleate and a semifluorinated alkane selected from 1-perfluorobutyl-pentane (F4H5) and 1-perfluorohexyl-octane (F6H8). In further embodiments, the pharmaceutical composition of the present invention essentially consists of timolol maleate and 1-perfluorohexyl-octane (F6H8), more specifically of timolol maleate suspended in 1-perfluorohexyl-octane (F6H8).

**[0083]** In exemplary embodiments, the pharmaceutical composition of the present invention consists of from about 90 to about 99.99% (w/w), more preferably from about 95 to about 99.9% (w/w), more preferably from 97 to 99% (w/w) even more preferably from 98 to 99% (w/w) of the liquid vehicle comprising a semifluorinated alkane as described above, preferably a semifluorinated alkane selected from F4H5 and F6H8, based on the weight of the final composition.

**[0084]** Liquid suspensions may be prepared by conventional methods. The solid timolol and/or pharmaceutically acceptable salt thereof, preferably timolol maleate or (S)-timolol-hemihydrate, more preferably timolol maleate, may be suspended in the liquid vehicle comprising the semifluorinated alkane. Alternatively, the particles of timolol and/or pharmaceutically acceptable salt thereof, preferably timolol maleate or (S)-timolol-hemihydrate, more preferably timolol maleate, may be precipitated in situ by adding a—typically organic—solution of the active ingredient (and, optionally, one or more solid excipients) under controlled conditions to the semifluorinated alkane-based vehicle.

**[0085]** Conventional grinding or milling methods using standard equipment such as a ball mill, hammer mill, roller mill, colloidal mill, jet mill, or the like may be used. If the particle size is to be reduced after preparation of a suspension, ultrasonication as well as various types of homogenisers may be used, such as colloid mills or high-pressure homogenisers.

**[0086]** In a preferred embodiment, the particle sizes of timolol and/or pharmaceutically acceptable salt thereof, preferably timolol maleate or (S)-timolol-hemihydrate, more preferably timolol maleate, when provided in form of a liquid suspension, are adjusted by first combining the drug particles with a liquid vehicle comprising or consisting of a semifluorinated alkane such as described in any one of the above embodiments, followed by a step of milling or grinding according to any of the above methods.

**[0087]** The pharmaceutical composition in suspended form in a liquid vehicle comprising a semifluorinated alkane provides several advantageous properties over conventional, aqueous or not semifluorinated alkane-based formulations, especially with respect to topical administration for ophthalmic use. For example, when conventional perfluorinated compounds are used as liquid vehicles, the suspensions tend to separate very rapidly by flotation of the dispersed phase, or by its sedimentation, depending on the relative densities of the dispersed phase and of the continuous phase. This is accompanied by a rapid formation of particle aggregates which may be dense and poorly re-dispersible. Rapid flotation or sedimentation makes precise and reproducible dosing very challenging, if not impossible. For example, if an ophthalmic suspension settles very rapidly after shaking, the first dosing from a full container, if not withdrawn immediately upon shaking, will contain a lower-than-intended number of drug particles, unless the container is held upside down, in which case more than the intended quantity of drug particles will be dispensed. When the same container is nearly empty and the last doses are dispensed, the drug dose withdrawn per volume will be too high if it was low in the beginning, and vice versa.

**[0088]** Moreover, aggregates may easily obstruct the dispensing channels or openings of containers and thereby lead to erroneous dosing. If dispensed from the container, they may cause irritation of the conjunctiva or of the cornea, depending on their size, shape and hardness.

**[0089]** In contrast, the semifluorinated alkane-based suspensions comprising timolol and/or a pharmaceutically acceptable salt thereof according to some embodiments of the invention remain finely dispersed and homogeneous. If flotation or sedimentation takes place, it occurs slowly, leaving sufficient time for the patient to withdraw a dose after shaking the container. The formation of large aggregates is not observed. After flotation or sedimentation, the drug particles are easily re-dispersed by gentle shaking, and appear to largely retain their original particle size distribution. Preferably, the pharmaceutical composition of the present invention is a suspension, wherein the particles of timolol and/or a pharmaceutically acceptable salt, preferably timolol maleate, are re-dispersible, for example by gentle shaking.

**[0090]** These properties of semifluorinated alkane-based suspensions of timolol and/or pharmaceutically acceptable salt thereof result in superior pharmaceutical quality and performance characteristics for the use of timolol in for example the treatment of ocular diseases. The level of

convenience to the patient and/or health care provider is greatly increased. More importantly, the dosing accuracy, i.e. precision and reproducibility of dosing, is greatly improved over other types of pharmaceutical suspensions. This will bring about a more reliable therapeutic effect and a reduced risk of adverse effects which result from overdosing.

**[0091]** A further surprising advantage of the presently described-compositions in form of suspensions of timolol or and/or a pharmaceutically acceptable salt thereof suspended in a semifluorinated alkane is that they appear to form very small droplets when dispensed from a dropper such as an eye dropper. Without wishing to be bound by theory, it is believed that the small droplet size is a result of an interplay of the semifluorinated alkane's unique properties in terms of their density, viscosity, and surface tension. In any case, it is believed that for topical administration into an eye a small drop or volume of administration is highly advantageous as the capability of the lacrimal sac to accept and hold fluid is extremely limited. In fact, it is very common that the administration of a conventional eye drop formulation based on water or oil immediately leads to a discharge of a substantial fraction of the administered medicine as well as some tear fluid. At the same time, there is a risk that some of the administered dose will be taken up systemically via the nasolacrimal duct. Hence, if an effective dose of an active ingredient can be incorporated in a small volume of liquid which can be dispensed as a very small droplet, this should also contribute to a substantially increased dosing reliability and reproducibility, thus enhancing the safety and effectiveness of the therapy.

**[0092]** A yet further advantage of the invention which is based on the use of semifluorinated alkanes is that they can be designed or mixed for an optimally adjusted evaporation behaviour after administration. Thus, it is possible to formulate for example an ophthalmic composition which delivers timolol or a salt thereof efficiently to the eye in such a way that the liquid vehicles is subsequently eliminated via evaporation. This is in sharp contrast to oily or perfluorinated eye drop vehicles which do easily not evaporate and thus form non-physiological residues at the site of administration, e.g. in the lacrimal sac.

**[0093]** In a second aspect, the present invention provides the pharmaceutical composition according to the first aspect of the invention, namely pharmaceutical composition comprising:

**[0094]** (a) timolol and/or a pharmaceutically acceptable salt thereof, and

**[0095]** (b) a liquid vehicle comprising a semifluorinated alkane for use as a medicament.

**[0096]** The pharmaceutical composition including all embodiments thereof as described above for the first aspect of the invention is especially useful for the therapy or prevention of diseases or conditions or any symptoms associated therewith related to an eye of a subject, preferably to an eye of a human subject.

**[0097]** The pharmaceutical composition of the present invention may be especially useful as an ophthalmic composition and may be administered to the eye of a subject. More specifically, the pharmaceutical composition of the present invention may be administered topically to the eye of a subject, for example to the eye lid, eye sac, eye surface and/or to an ophthalmic tissue of a patient. Preferably, the pharmaceutical composition of the present invention may be

topically administered to an outer surface of an eye of a patient or to an ophthalmic tissue which is readily accessible by the patient or by another person administering the pharmaceutical composition to the eye of the patient in need thereof.

**[0098]** The present pharmaceutical composition, especially when used as liquid of either low or higher viscosity (usually in the range of 1 to 3.5 mPa s) may advantageously be administered in form of drops or by spraying or by injection. Most preferably, however, the liquid pharmaceutical composition of the present invention, especially when provided in the form of a suspension, may be administered as drops, more specifically as eyedrops to be administered topically to the eye.

**[0099]** Depending on the extent of the disease, or whether or not both eyes of the patient to be treated are affected, the drops or eyedrops of the present ophthalmic pharmaceutical composition may be administered to only one eye or to both eyes of the patient. The present pharmaceutical composition may provide droplet sizes when administered from conventional droppers, with a volume usually in the range from about 5 to about 15  $\mu$ l. This small droplet size usually facilitates the dropwise administration and, moreover, facilitates precise dosage of the pharmaceutical composition of the present invention. Accordingly, the pharmaceutical composition of the present invention may be administered as single drops with a volume of about 5 to 15  $\mu$ l per dose per eye, preferably with a volume of about 8 to 15  $\mu$ l per dose per eye, more preferably with a volume of about 9 to 12  $\mu$ l per dose per eye, even more preferably with a volume of about 10 to 12  $\mu$ l per dose per eye and most preferably with a volume of about 11  $\mu$ l per dose per eye.

**[0100]** Depending on the need, the composition according to the present invention may be administered once (qd), twice (bid), three-times (tid) or four-times (qid) per day per eye. Preferably, the composition according to the present invention is administered up to two-times per day per eye. In a preferred embodiment, the composition of the present invention is administered twice (bid) daily. In a more preferred embodiment, the composition of the present invention is administered once (qd) daily.

**[0101]** The pharmaceutical composition according to the present invention is especially useful in the treatment of glaucoma, increased intraocular pressure (IOP), ocular hypertension and/or a symptom associated therewith.

**[0102]** The present invention provides stable liquid pharmaceutical compositions, especially stable liquid suspensions comprising timolol and/or a pharmaceutically acceptable salt thereof. These compositions can be topically administered and allow the administration of the active ingredient timolol in lower dosages compared to known liquid formulations, thereby reducing the side effects associated to the active ingredient and the additional components of said known liquid formulations, in particular in the treatment of glaucoma.

**[0103]** Based on this, the pharmaceutical composition for the use of the present invention allows for a significant reduction of droplet size and target dose volume as described above associated therewith and therefore, as outlined above, for a significant reduction of the total daily dose of timolol administered for use in the treatment of glaucoma, increased intraocular pressure, ocular hypertension and/or a symptom associated therewith. Accordingly, in a preferred embodiment the present pharmaceutical composition for use in the

treatment of glaucoma, increased intraocular pressure (IOP), ocular hypertension and/or a symptom associated therewith, comprises timolol and/or a pharmaceutically acceptable salt thereof, preferably timolol maleate, suspended in the liquid vehicle comprising a semifluorinated alkane at a concentration corresponding to a concentration of timolol free base of from 0.3 to 2.5% (w/v), preferably at a concentration of from 0.5 to 2.0% (w/v), more preferably of from about 0.5 to 1.5% (w/v). In said preferred embodiments, the liquid vehicle comprises or essentially consists of a semifluorinated alkane, as defined by Formula (II) or any one of the semifluorinated alkanes as defined above, such as a semifluorinated alkane selected from 1-perfluorobutyl pentane or 1-perfluorohexyl octane. In further embodiments, the pharmaceutical composition for the use according to the present invention may be administered in a dose volume per eye of 10 to 12  $\mu\text{l}$  wherein the timolol and/or a pharmaceutically acceptable salt thereof may be suspended in the liquid vehicle in a concentration of at least 0.3% (w/v), preferably of at least 0.5% (w/v).

**[0104]** In a preferred embodiment of the present invention, the single dose of timolol as free base administered per eye is from about 33 to about 280  $\mu\text{g}$ , preferably of from about 55 to about 220  $\mu\text{g}$ , more preferably of from about 55 to about 165  $\mu\text{g}$ , most preferably of from about 55 to about 150  $\mu\text{g}$ . In a more preferred embodiment, the pharmaceutical composition for use in the treatment of glaucoma, increased intraocular pressure (IOP), ocular hypertension and/or a symptom associated therewith comprises a) timolol maleate suspended in a semifluorinated alkane, preferably F6H8, wherein the dose of timolol, as a free base, administered per eye is from about 55 to about 165  $\mu\text{g}$ , more preferably from about 55 to about 150  $\mu\text{g}$ .

**[0105]** In another embodiment, the pharmaceutical composition for use in the treatment of glaucoma, increased intraocular pressure (IOP), ocular hypertension and/or a symptom associated therewith, may be administered to subjects concomitantly suffering from dry eye disease and/or hypertension and/or cardiac related diseases. Thus, the pharmaceutical composition for use in the treatment of glaucoma, increased intraocular pressure (IOP), ocular hypertension and/or a symptom associated therewith, is effective in not exacerbating comorbidities such as dry eye disease and/or hypertension and/or cardiac related diseases.

**[0106]** In another preferred embodiment, the pharmaceutical composition for use in the treatment of glaucoma, increased intraocular pressure (IOP), ocular hypertension and/or a symptom associated therewith is effective in reducing side effects derived from the treatment of glaucoma or ocular hypertension with non-selective beta blockers at higher dosages, wherein said side effects are exacerbation of chronic obstructive airways disease and/or bronchospasm and/or dry eye symptoms.

**[0107]** In a third aspect, the present invention provides a method for the treatment of glaucoma, increased intraocular pressure, ocular hypertension and/or a symptom associated therewith, comprising administering to the eye of a subject in need thereof a pharmaceutical composition according to the first aspect of the invention, namely a pharmaceutical composition comprising:

**[0108]** (a) timolol and/or a pharmaceutically acceptable salt thereof, and

**[0109]** (b) a liquid vehicle comprising a semifluorinated alkane.

**[0110]** Accordingly, the method according to this aspect of the present invention comprises:

**[0111]** providing a composition comprising:

**[0112]** (a) timolol and/or a pharmaceutically acceptable salt thereof, and

**[0113]** (b) a liquid vehicle comprising a semifluorinated alkane, and

**[0114]** topically administering said composition to a surface of the eye of the subject, or the patient.

**[0115]** It should be noted that for the method according to this aspect of the invention all embodiments and preferred embodiments as described above in connection with the other aspects of the invention apply respectively. The subject, or patient in one embodiment may be a human. In another embodiment, the subject may be a veterinary subject or patient.

**[0116]** In yet a further aspect, the present invention provides for the use of the pharmaceutical composition according to the first aspect of the invention, namely a pharmaceutical composition comprising:

**[0117]** (a) timolol and/or a pharmaceutically acceptable salt thereof, and

**[0118]** (b) a liquid vehicle comprising a semifluorinated alkane

**[0119]** for the manufacture of a medicament for the treatment of glaucoma, increased intraocular pressure, ocular hypertension and/or a symptom associated therewith. It should be noted that for the manufacture of a medicament according to this aspect of the invention, all embodiments and preferred embodiments as described above in connection with the other aspects of the invention apply respectively.

**[0120]** In yet a further aspect, the present invention provides a pharmaceutical kit comprising the composition as described above in connection with any aspect of the invention, namely a pharmaceutical composition comprising:

**[0121]** (a) timolol and/or a pharmaceutically acceptable salt thereof, and

**[0122]** (b) a liquid vehicle comprising a semifluorinated alkane,

**[0123]** and a container adapted for holding the pharmaceutical composition. Preferably, the container which contains the pharmaceutical composition of the present invention further comprises a drop dispenser or device adapted for administering the pharmaceutical composition.

**[0124]** In specific embodiments of the kit according to this aspect of the present invention, the container has a dispensing means such as a dropping device adapted for topically administering the composition to the eye of a subject or patient, more specifically dispensing means for dropwise topical administration to a surface of the eye of a subject or patient. In one of the preferred embodiments, the dispensing means is adapted to dispense the pharmaceutical composition dropwise in volumes of less than about 15  $\mu\text{l}$  per drop. In further embodiments, the dispensing means is adapted to dispense drops having a volume of less than about 13  $\mu\text{l}$ , 12  $\mu\text{l}$ , or 11  $\mu\text{l}$ , respectively. In particular, drop volumes of less than 12  $\mu\text{l}$  are presently considered very useful in view of the limited holding capacity of one of the preferred sites of administration, the front of the eye. For the avoidance of doubt, such small droplet sizes are primarily enabled by the incorporation of the semifluorinated alkane (or semifluorinated alkanes) according to the invention, and common droppers for eye drops which normally deliver aqueous

drops of about 30 to 60  $\mu\text{l}$  are capable of dispensing much smaller drops of semifluorinated alkanes-based formulations.

**[0125]** In the kit according to this aspect of the invention, the container may hold a single dose or a plurality of doses of the present pharmaceutical composition comprising timolol and/or a pharmaceutically acceptable salt thereof and a liquid vehicle comprising a semifluorinated alkane as described above.

**[0126]** Furthermore, the kit according to this aspect of the invention may further comprise instructions for use of the container for dropwise topical administration of the composition to a surface of the eye of a patient. The instructions or directions for use preferably comprised by the kit according to this aspect of the invention may be in any form suited to instruct the user how to perform the topical administration to the affected eye of the patient or subject. It may be in any readable or tangible form, preferably in printed form or in any machine- or computer-readable form preferably in form of a machine-readable optical label such as, for example, a barcode or a QR-code. In a particularly preferred embodiment the directions for use are provided in form of an instruction leaflet, product or package insert or as an enclosed label.

**[0127]** The following are numbered items comprised by the present invention:

**[0128]** 1. A pharmaceutical composition comprising:

**[0129]** (a) timolol and/or a pharmaceutically acceptable salt thereof;

**[0130]** (b) a liquid vehicle comprising a semifluorinated alkane.

**[0131]** 2. The pharmaceutical composition according to item 1, comprising a semifluorinated alkane of the formula (II)



**[0132]** wherein

**[0133]** n is an integer from 3 to 7, and

**[0134]** m is an integer from 4 to 7;

**[0135]** or

**[0136]** wherein

**[0137]** n is an integer from 2 to 10, and

**[0138]** m is an integer from 2 to 10

**[0139]** 3. The pharmaceutical composition of item 1 or 2, wherein the semifluorinated alkane is selected from the group consisting of 1-perfluorobutyl-pentane ( $\text{CF}_3(\text{CF}_2)_3(\text{CH}_2)_4\text{CH}_3$ ; F4H5), 1-perfluorohexyl-octane ( $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ ; F6H8), 1-perfluorohexyl-hexane ( $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_5\text{CH}_3$ ; F6H6) and 1-perfluorohexyl-decane ( $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_9\text{CH}_3$ ; F6H10), preferably one selected from the group consisting of 1-perfluorobutyl-pentane ( $\text{CF}_3(\text{CF}_2)_3(\text{CH}_2)_4\text{CH}_3$ ; F4H5), and 1-perfluorohexyl-octane ( $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ ; F6H8).

**[0140]** 4. The pharmaceutical composition of any preceding item, wherein the liquid vehicle comprises a co-solvent.

**[0141]** 5. The pharmaceutical composition of any preceding item, wherein the liquid vehicle comprises at least 85% (w/w) of a semifluorinated alkane or a mixture of different semifluorinated alkanes.

**[0142]** 6. The pharmaceutical composition of any preceding item, wherein the liquid vehicle essentially consists of a semifluorinated alkane or a mixture of different semifluorinated alkanes.

**[0143]** 7. The pharmaceutical composition of any preceding item, wherein timolol and/or a pharmaceutically acceptable salt thereof is suspended in the liquid vehicle comprising a semifluorinated alkane.

**[0144]** 8. The pharmaceutical composition of any preceding item, wherein component a) is timolol maleate.

**[0145]** 9. The pharmaceutical composition of any preceding item, wherein the concentration of timolol free base is from about 0.3 to about 2.5% (w/v).

**[0146]** 10. The pharmaceutical composition of any preceding item, wherein component a) is timolol maleate suspended in b) the liquid vehicle.

**[0147]** 11. The pharmaceutical composition of any preceding item, wherein the composition is essentially free of water and/or a preservative.

**[0148]** 12. The composition of any preceding item, wherein the composition is free of further excipients.

**[0149]** 13. The composition of any preceding item, wherein the composition is free of a surfactant.

**[0150]** 14. The pharmaceutical composition of any preceding item, comprising timolol in form of timolol maleate and a semifluorinated alkane selected from 1-perfluorobutyl-pentane (F4H5) and 1-perfluorohexyl-octane (F6H8).

**[0151]** 15. The pharmaceutical composition of any preceding items, wherein the composition comprises a) timolol in form of timolol maleate and b) 1-perfluorohexyl-octane (F6H8).

**[0152]** 16. The pharmaceutical composition of any of item 7 to 15, wherein at least about 90% of the suspended particles of timolol and/or a pharmaceutically acceptable salt thereof have a size of not more than about 15  $\mu\text{m}$ .

**[0153]** 17. The pharmaceutical composition of any of item 7 to 16, wherein at least about 90% of the suspended particles of timolol and/or a pharmaceutically acceptable salt thereof have a size of not more than about 15  $\mu\text{m}$  after three weeks of storage at room temperature.

**[0154]** 18. The pharmaceutical composition of any preceding item for use as a medicament.

**[0155]** 19. The pharmaceutical composition for use according to item 18, for the treatment of glaucoma, increased intraocular pressure, ocular hypertension and/or a symptom associated therewith.

**[0156]** 20. The pharmaceutical composition for use according to item 18 or 19, wherein the composition is administered to the eye of a subject.

**[0157]** 21. The pharmaceutical composition for use according to any of items 18 to 20, wherein the composition is administered topically to the eye of a subject.

**[0158]** 22. The pharmaceutical composition for the use according to any of items 18 to 21, wherein the pharmaceutical composition is administered in a dose volume per eye of from about 8 to about 15  $\mu\text{l}$ , preferably from about 10 to about 12  $\mu\text{l}$ .

**[0159]** 23. The pharmaceutical composition for the use according to any of items 18 to 22, wherein the concentration of timolol as free base is of from about 0.3 to about 2.5% (w/v), preferably of from about 0.5 to about 2.0% (w/v), more preferably of from about 0.5 to 1.5% (w/v).

**[0160]** 24. The pharmaceutical composition for the use according to any of items 18 to 23, wherein timolol and/or a pharmaceutically acceptable salt thereof is suspended in the liquid vehicle.

- [0161] 25. The pharmaceutical composition for the use according to any of items 18 to 24, wherein the composition is administered up to four times daily, preferably the composition is administered twice daily, more preferably once daily.
- [0162] 26. A method for the treatment of glaucoma, increased intraocular pressure, ocular hypertension and/or a symptom associated therewith, comprising administering to the eye of a subject in need thereof a pharmaceutical composition according to any one of items 1 to 17.
- [0163] 27. The use of a pharmaceutical composition of any of items 1 to 17 for the manufacture of a medicament for the treatment of glaucoma, increased intraocular pressure, ocular hypertension and/or a symptom associated therewith.
- [0164] 28. A kit comprising the pharmaceutical composition according to any one of items 1 to 17 and a container for holding the pharmaceutical composition.
- [0165] 29. The kit according to item 28, wherein the container comprises a drop dispenser for administering the pharmaceutical composition.
- [0166] 30. The kit according to item 29, wherein the container comprises dispensing means for dropwise topical administration to a surface of the eye of a patient, said dispensing means preferably being adapted to dispense the composition dropwise in volumes of less than about 15  $\mu\text{l}$ .
- [0167] 31. The kit according to any of item 28 to 30, wherein the container holds a single dose or a plurality of doses of the composition of any of claims 1 to 17.
- [0168] 32. The kit according to any of items 28 to 31, further comprising instructions for use of the container for dropwise topical administration of the composition to a surface of the eye of a patient.
- [0169] 33. A method of treating glaucoma, increased intraocular pressure, ocular hypertension or a symptom associated therewith, the method comprising administering to an eye of a human with glaucoma, increased intraocular pressure, ocular hypertension or a symptom associated therewith, a composition comprising a) timolol and/or a pharmaceutically acceptable salt thereof and b) a liquid vehicle comprising a semifluorinated alkane, wherein timolol and/or a pharmaceutically acceptable salt thereof is preferably suspended in the liquid vehicle, wherein said method is therapeutically effective in treating glaucoma, increased intraocular pressure, ocular hypertension or a symptom associated therewith.
- [0170] 34. The method according to item 33, wherein component a) is timolol maleate and wherein the concentration of timolol free base is of from about 0.3 to 2.5% (w/v), preferably of from about 0.5 to 2.0% (w/v), more preferably of from about 0.5 to about 1.5% (w/v).
- [0171] 35. The method according to any one of items 33 to 34, wherein the composition target dose volume per eye is from about 10 to about 12  $\mu\text{l}$ , preferably about 11  $\mu\text{l}$ .
- [0172] 36. The method according to any of items 33 to 35, wherein the semifluorinated alkane is selected from F6H8 and F4H5.
- [0173] 37. The method according to item 36, wherein the semifluorinated alkane is F6H8.
- [0174] 38. The method according to any one of items 33 to 37, wherein the composition is administered up to twice daily, preferably once daily.

- [0175] 39. The method according to any one of items 33 to 38, wherein the composition is substantially free of water and of preservative.

#### DESCRIPTION OF THE DRAWINGS

[0176] FIG. 1 is a graphical representation of the results of the measurement of the in-vivo intraocular pressure after administration once a day of a suspension of timolol at a concentration of 0.5% (w/v) in 1-perfluorohexyl-octane (F6H8) versus a formulation of timolol in aqueous solution with a concentration of 0.5% (w/v). The graph shows the chronological progression of the mean intraocular pressure (IOP) as measured in mmHg.

[0177] FIG. 2 is a graphical representation of the results of the measurement of the in-vivo intraocular pressure after administration once a day of a suspension of timolol at a concentration of 1.37% (w/v) in 1-perfluorohexyl-octane (F6H8) versus a formulation of timolol in aqueous solution with a concentration of 0.5% (w/v). The graph shows the chronological progression of the mean intraocular pressure (IOP) as measured in mmHg.

[0178] FIG. 3 is a graphical representation of the results of the measurement of the in-vivo intraocular pressure after administration twice a day of a suspension of timolol at a concentration of 0.5% (w/v) in 1-perfluorohexyl-octane (F6H8) versus a formulation of timolol in aqueous solution with a concentration of 0.5% (w/v). The graph shows the chronological progression of the mean intraocular pressure (IOP) as measured in mmHg.

#### Examples

[0179] The following examples serve to illustrate the invention; however, these are not to be understood as restricting the scope of the invention.

##### Example 1: Preparation of Timolol Suspensions

[0180] 109.34 mg of timolol maleate, CAS number 26921-17-5 (LKT Labs; purity 99.5%) were introduced to a 25 mL vessel, filled with stainless steel balls, diameter 2 mm. Afterwards, 8 mL of 1-perfluorohexyl-octane (F6H8) were added, the vessel was closed and the milling was performed with a planetary ball mill (PM 100, Retsch GmbH Germany) for 3 hours at 150 rpm with an interval of 10 minutes (with change of direction). After the milling, the thereby formed suspension was transferred into a glass vial, shaken on a Vortex shaker for a minimum of 30 seconds, and sealed. Considering that 1.3668 mg timolol maleate correspond to 1.0 mg timolol free base, a 1.0% (w/v) Timolol suspension (10 mg/mL) in F6H8 was obtained.

[0181] Following the same procedure as described above, a 15 mg/ml timolol suspension was prepared.

[0182] A suspension with the concentration 5 mg/mL was diluted out of the 10 mg/mL stock suspension by diluting the suspension with F6H8.

[0183] The 10 mg/mL timolol suspension was stored in a glass vial at room temperature and the particle size distribution (PSD) was determined by Laser diffraction (HELOS 2412, performed with a 50 mL cuvette). Table 1 below shows the particle size distributions for different Timolol suspensions after storage at room temperature (RT).

TABLE 1

Formulation	X <sub>50</sub> (μm)	X <sub>90</sub> (μm)	X <sub>99</sub> (μm)	Conditions of storage
Particle size by laser diffraction (Helos H2412) performed with 50 mL cuvette and R2 lenses. (R2 lenses measurement range 0.25-87.5 μm)				
5 mg/mL Timolol in F6H8	6.02	10.37	15.53	2 days storage at RT
10 mg/mL Timolol in F6H8	5.80	10.23	15.83	3 days storage at RT
15 mg/mL Timolol in F6H8	6.35	11.25	16.53	3 days storage at RT
Particle size by laser diffraction (Helos H2412) with ultrasound treatment. Performed with 50 mL cuvette and R1 lenses. (R1 lenses measurement range 0.18-35 μm)				
5 mg/mL Timolol in F6H8	3.22	3.94	4.18	2 days storage at RT
10 mg/mL Timolol in F6H8	3.18	3.92	4.17	5 days storage at RT
15 mg/mL Timolol in F6H8	3.15	3.89	4.17	5 days storage at RT

**[0184]** X<sub>50</sub>: median particle diameter determined on a volumetric basis, i.e. 50% by volume of the particles are smaller than the given diameter and 50% are larger.

**[0185]** X<sub>90</sub>: particle diameter corresponding to 90% of the cumulative undersize distribution determined on a volumetric basis, i.e. 90% of the particles have a diameter lower than the given value X<sub>0</sub>.

**[0186]** X<sub>99</sub>: particle diameter corresponding to 99% of the cumulative undersize distribution determined on a volumetric basis, i.e. 99% of the particles have a diameter lower than the given value X<sub>99</sub>.

**[0187]** All Timolol suspensions in pure F6H8 with concentrations of 5 mg/ml, 10 mg/ml and 15 mg/ml, prepared by a ball milling process as described above, showed an optical appearance, homogeneity of the suspension and a suitability for re-homogenization of the settled suspensions which were ranked positive for preclinical studies in animal models.

#### Example 2: Measurement of Intraocular Pressure (IOP) in an Animal Study

**[0188]** An animal study utilizing 8 normotensive dogs was carried out in order to assess the pharmacodynamics of a composition comprising Timolol and a semifluorinated alkane with regard to its capability to lower the IOP (intraocular pressure) in comparison with a commercial solution of Timolol which is administered in form of an aqueous solution. The study setup and design was as follows.

**[0189]** The dogs were selected for participation in the study based on overall health, body weight, results of ophthalmic examinations, response to IOP challenge, and the following criteria:

- [0190]** healthy, normal ocular surface;
- [0191]** no invasive ocular procedures for at least one month prior to the study; particularly procedures involving the cornea or ocular anterior segment in general;
- [0192]** no topical or systemic corticosteroid treatment for at least one month;
- [0193]** washout from prior topical ocular study medication commensurate with the typical washout period used for clinical studies (at least one week)

**[0194]** The study was performed according to the plan as summarized in Table 2 below. The topical ocular dose of the respective Timolol aqueous solution or Timolol-suspension was administered to the central or superior part of the cornea via a micropipette and allowed to spread across the surface of the eye. After the dose was administered, the eye was allowed to close naturally. Each animal was restrained for approximately one minute to prevent rubbing of the eyes.

TABLE 2

Topical Ocular Dose Regime		Target Dose Level (μg/eye)	Target Dose Volume	Dose
OD	OS	OD	OS (μL/eye)	Frequency
Timolol 0.5% (5 mg/mL)*	Timolol in F6H8 (5 mg/mL)	150	55 11 (OS) 30 (OD)	QD for 8 days
Topical Ocular Dose Regime		Target Dose Level (μg/eye)	Target Dose Volume	Dose
OS	OD	OS	OD (μL/eye)	Frequency
Timolol 0.5% (5 mg/mL)*	Timolol in F6H8 (13.7 mg/mL)	150	150 11 (OD) 30 (OS)	QD for 8 days

\*aqueous solution  
OD: right eye  
OS: left eye  
QD: once daily  
BID: twice daily

**[0195]** In a first study, as schematized in Table 2, a suspension of Timolol (5 mg/mL) in F6H8 was administered to the left eye versus an aqueous solution of Timolol (5 mg/mL), which was administered to the right eye. The intraocular pressure (IOP) was measured at 0 (immediately pre-dose), 2, 4 and 6 hours post-dose on days 1, 2, 3, 6 and 7; at -1, 0 (immediately pre-dose), 1, 2, 4, 6, 24 and 48 hours post-dose on day 8 using a tonometer (TonoVet). Three readings per eye were taken. The results are summarized in FIG. 1 showing the development of the mean intraocular pressure (IOP) during treatment as described above.

**[0196]** In a second study, as schematized in Table 2, a suspension of Timolol (13.7 mg/mL) in F6H8 was administered to the right eye versus an aqueous solution of Timolol (5 mg/mL) which was administered to the left eye. The intraocular pressure (IOP) was measured at 0 (immediately pre-dose), 2, 4 and 6 hours post-dose on days 1, 2, 3, 6 and 7; at -1, 0 (immediately pre-dose), 1, 2, 4, 6, 24 and 48 hours post-dose on day 8, using a tonometer (TonoVet). Three readings per eye were taken. The results are summarized in FIG. 2 showing the development of the mean intraocular pressure (IOP) during treatment as described above.

**[0197]** In a third study, 11 μl of a suspension of Timolol (5 mg/mL) in F6H8 were administered twice a day for 8 days to the left eye versus 30 μl of an aqueous solution of Timolol (5 mg/mL), which was administered to the right eye. The intraocular pressure (IOP) was measured at 0 (immediately pre-dose), 2, 4 and 6 hours post-dose on days 1, 2, 3, 6 and 7; at -1, 0 (immediately pre-dose), 1, 2, 4, 6, 24 and 48 hours post-dose on day 8, using a tonometer (TonoVet). Three readings per eye were taken. The results are summarized in

FIG. 3 showing the development of the mean intraocular pressure (IOP) during treatment as described above.

**[0198]** The compositions according to the present invention showed a decrease of the intraocular pressure.

1. A pharmaceutical composition comprising:

(a) timolol and/or a pharmaceutically acceptable salt thereof and

(b) a liquid vehicle comprising a semifluorinated alkane.

2. The pharmaceutical composition according to claim 1, wherein the semifluorinated alkane has formula (II)



wherein

n is an integer from 3 to 7, and

m is an integer from 4 to 7.

3. The pharmaceutical composition of claim 1, wherein the semifluorinated alkane is selected from the group consisting of 1-perfluorobutyl-pentane ( $\text{CF}_3(\text{CF}_2)_3(\text{CH}_2)_4\text{CH}_3$ ; F4H5) and 1-perfluorohexyl-octane ( $\text{CF}_3(\text{CF}_2)(\text{CH}_2)_7\text{CH}_3$ ; F6H8).

4. The pharmaceutical composition of claim 1, wherein the timolol and/or a pharmaceutically acceptable salt thereof is suspended in the liquid vehicle comprising the semifluorinated alkane.

5. The pharmaceutical composition of claim 1, wherein the concentration of timolol as free base is from about 0.3 to about 2.5% (w/v).

6. The pharmaceutical composition of claim 5, wherein the concentration of timolol as free base is from about 0.5 to about 2.0% (w/v).

7. The pharmaceutical composition of claim 1, comprising timolol in the form of timolol maleate.

8. The pharmaceutical composition of claim 4, wherein at least about 90% of the suspended particles of timolol and/or a pharmaceutically acceptable salt thereof have a size of not more than about 15  $\mu\text{m}$ .

9. (canceled)

10. A method for the treatment of glaucoma, increased intraocular pressure, ocular hypertension and/or a symptom associated therewith, in a patient in need thereof, comprising administering to said patient a pharmaceutical composition according to claim 1.

11. The method according to claim 10, wherein the composition is administered to the eye of a subject up to four times daily.

12. The method according to claim 10, wherein the pharmaceutical composition is administered in a dose volume per eye of from about 8 to about 15  $\mu\text{l}$ .

13. The method according to claim 10, wherein the semifluorinated alkane is 1-perfluorohexyl-octane ( $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ , F6H8).

14. The pharmaceutical composition according to claim 1, further comprising a co-solvent.

15. A kit comprising the pharmaceutical composition according to claim 1 and a container for holding the pharmaceutical composition.

16. The pharmaceutical composition of claim 5, wherein the concentration of timolol as free base is from about 0.5 to about 1.5% (w/v).

17. The pharmaceutical composition of claim 7, wherein the composition comprises the timolol maleate at a concentration of from about 0.4 to about 3.4% (w/v).

18. The pharmaceutical composition of claim 17, wherein the composition comprises the timolol maleate at a concentration of from about 0.68% to about 2.1% (w/v).

19. The method according to claim 10, wherein the composition is administered to the eye of a subject once daily.

20. The method according to claim 10, wherein the pharmaceutical composition is administered in a dose volume per eye of from about 10 to about 12  $\mu\text{l}$ .

\* \* \* \* \*