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(54) Title: OPHTHALMIC PHARMACEUTICAL COMPOSITION CONTAINING A CARBONIC ANHYDRASE INHIBITOR AND METHOD FOR THE PREPARATION THEREOF

(57) Abstract: The present invention relates to a stable pharmaceutical formulation for topical administration containing a therapeutically effective quantity of Brinzolamide or ophthalmologic acceptable salts thereof and an effective quantity of a surfactant such as poloxamer, to be used for the treatment of ocular hypertension and glaucoma.

WO 2013/139444 A1

OPHTHALMIC PHARMACEUTICAL COMPOSITION CONTAINING A CARBONIC ANHYDRASE INHIBITOR AND METHOD FOR THE PREPARATION THEREOF

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a stable ophthalmic pharmaceutical formulation comprising a therapeutically effective quantity of a carbonic anhydrase inhibitor such as Brinzolamide or a pharmaceutical acceptable salt thereof and an effective quantity of a surfactant capable of maintaining physical and chemical stability of the active substance in the finished dosage form and a method for the preparation thereof.

BACKGROUNG OF THE INVENTION

Glaucoma is a disease, usually caused by high intraocular pressure, which leads to disruption of normal eye function and subsequently, degeneration of the eye. The damage can be extended to the optic nerve head and result in irreversible loss of the eyesight and if left untreated it could lead to irreversible blindness. Nowadays, it is believed by the majority of ophthalmologists that the increased intraocular pressure (also known as ocular hypertension) is the earliest phase in the onset of glaucoma. Later symptoms include optic nerve head damage and the characteristic glaucomatous visual effects.

The early methods for the treatment of glaucoma included the drug Pilocarpine, which produced undesired local side effects. More recently new regimes have been employed for the treatment of ocular hypertension and glaucoma.
It is known that carbonic anhydrase inhibitors are used for the treatment of ocular hypertension related to glaucoma. The drugs that belong to this family inhibit the enzyme carbonic anhydrase and thus, reduce the contribution of the aqueous humor formation made by the carbonic anhydrase pathway. However, these drugs cannot be used via a systemic route because then, they inhibit the enzymatic activity of carbonic anhydrase throughout the entire body. In general, the enzyme carbonic anhydrase plays a major role in regulating pH and fluid levels in the human body by converting carbon dioxide to carbonic acid and bicarbonate ions.

Targeting of the carbonic anhydrase inhibitor to the desired ocular tissue diminishes or even eliminates the side effects caused by the inhibition of carbonic anhydrase in the entire body, which can be as a severe as metabolic acidosis or less severe, like numbness, vomiting, tingling, general malaise and the like.

Brinzolamide, a carbonic anhydrase inhibitor, is the chemical molecule designated as (R)-4-ethylamino-3, 4-dihydro-2-(3-methoxy) propyl-2H-thieno[3, 2-e]-1, 2-thiazine-6- sulfonamide 1, 1 dioxide. It has been found to reduce intraocular pressure with fewer side effects compared to the earlier glaucoma treatments. Brinzolamide is a white to almost white powder with a melting point at 131°C. Furthermore, is insoluble in water and slightly soluble in alcohol and methanol.

Various methods are already known for the industrial preparation of dosage forms comprising a carbonic anhydrase inhibitor and especially Brinzolamide or salt thereof, as an active ingredient due to its useful therapeutical properties. However, according to prior art, substantial difficulties are encountered in the production of stable ophthalmic formulations due to the poor solubility of said active ingredient.

EP-B- 941 094 discloses a process for the preparation of Brinzolamide suspension and the use of Tyloxapol® and Triton® X-100 as a surfactant.

EP-A-2 394 637 discloses a process for the manufacture of sterile ophthalmic suspensions comprising Brinzolamide, characterized in that it comprises a step of sterilization of Brinzolamide by gamma irradiation or ethylene oxide.

Although each of the above patents represents an attempt to overcome the low aqueous solubility problems associated with topical pharmaceutical compositions comprising Brinzolamide, a need still exists for the development of a stable ophthalmic product that will overcome the deficiencies of the prior art.

SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide a stable ophthalmic formulation for topical administration containing a carbonic anhydrase inhibitor and in particular Brinzolamide or ophthalmological acceptable salts thereof to be used for the treatment of ocular hypertension and glaucoma, which overcomes the deficiencies of the prior art.

Moreover, an aspect of the present invention is to provide a formulation for topical administration to the eye, containing Brinzolamide or ophthalmological acceptable salts thereof, which is bioavailable and effective with sufficient self-life and good pharmacotechnical properties.

Another aspect of the present invention is to provide a method for the preparation of a stable ophthalmic formulation for topical administration comprising a carbonic anhydrase inhibitor and in particular Brinzolamide or ophthalmological acceptable salts thereof, as the active ingredient, permitting adequate release of the active medicament that can be used for the treatment of ocular hypertension and glaucoma with improved pharmacotechnical characteristics of the composition and in particular adequate suspendability of the active ingredient within the finished dosage form.

In accordance with the above, the present invention provides an ophthalmic pharmaceutical composition for topical administration comprising a carbonic anhydrase inhibitor, such as Brinzolamide or ophthalmological acceptable salts thereof, as the active ingredient and an effective amount of a surfactant, such as Poloxamer in order to provide adequate solubilization and stabilization of the low soluble active ingredient in the aqueous formulations.

According to another embodiment of the present invention, a process for the preparation of a stable ophthalmic composition for topical administration for the treatment of ocular hypertension and glaucoma, comprising a carbonic anhydrase inhibitor, such as Brinzolamide or ophthalmologic acceptable salts thereof, as the active ingredient and an effective amount of a surfactant agent, such as Poloxamer in order to provide adequate solubilization and stabilization of the low soluble active ingredient in the aqueous formulations is provided, wherein it comprises the following steps:

- First forming a solution of the surfactant in water for injection;
- Then adding to the solution the total quantity of Brinzolamide;

- Autoclaving the above mixture and immediately homogenize until ambient temperature is reached;
- Passing the solution through colloidal mill to reach the desired particle size;
- Subsequently, forming a second solution in water for injection by adding at least one tonicity agent, suspending agent, chelating agent and preservative agent and mixing until complete homogeneity;
- adjusting the pH of the second solution by adding NaOH or HCL;
- autoclaving the obtained solution and subsequently homogenize until ambient temperature is reached;
- Mixing gradually the two formed solutions until uniform, and
- Finally, adjusting the final mixture with water for injection and filling in appropriate container.

Further preferred embodiments of the present invention are defined in dependent claims 2 to 6 and 8 to 10.
Other objects and advantages of the present invention will become apparent to those skilled in the art in view of the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

A stable ophthalmic solution for topical administration needs to fullfill specific characteristics, for example pH value, osmolality, specific gravity and viscosity. Regulation of these characteristics through the selection of specific excipients will avoid any unwanted side effects such as visual blurring, burning sensation, low corneal contact and drying of the eye.

In particular, the viscosity of the ophthalmic solution should be regulated so as to benefit of increasing the ocular contact time, thereby increasing the drainage rate and increasing drug bioavailability. A secondary benefit is a lubricant effect that is noticeable to many patients. In addition, viscosity serves to retard the settling of the particles between uses and at the same time maintains their suspension for uniform dosing.
Further, an ophthalmic solution should meet the stability and the sterilization issues.

A major object of the present invention is to provide a stable pharmaceutical formulation for ophthalmic use containing a carbonic anhydrase inhibitor and in particular Brinzolamide or ophthalmologically acceptable salts thereof. All pharmaceutical dosage forms should have impurities at very low levels, as said impurities might be toxic and harmful for the humans. Moreover, the impurities diminish the potency of pharmaceutical compositions during storage. They can also act as catalysts or intermediates in chemical reactions and change the drug into another form.

According to the present invention it has been found that a Brinzolamide ophthalmic composition is more stable and thus more potent when a surfactant, such as Poloxamer is used.

The surface or interfacial tension produced by polyethoxylated non-ionic surfactants at the concentration so that they form aggregates is usually higher compared to that of ionic surfactants, thus making the non-ionic surfactants less destructive on cell membranes and less irritating and toxic. In addition, the non-ionic surfactants are usually more bulky in size, less polar and less preferentially adsorbed at the surface, therefore, they have a tendency to associate together at a much lower concentration to reduce the surface free energy.

In addition, the concentration of Poloxamer 407 has been optimized, as when the concentration of a nonionic surfactant exceeds a certain level above the CMC (critical micelle concentration), the antimicrobial effectiveness of the preservative such as Benzalkonium Chloride is reduced. An effective quantity according to the present invention is from about 0.01% to 0.05% in the total volume of the finished dosage form.

Poloxamer is a non-ionic poly(ethylene oxide) (PEO)–poly(propylene oxide) (PPO) copolymer. It is used in pharmaceutical formulations as surfactant, emulsifying agent, solubilizing agent, dispersing agent, and in vivo absorbance enhancer. It is available in several grades differing in molecular weight and composition of the hydrophilic PEO block (a) and hydrophobic PPO block (b). In addition, the concentration of Poloxamer in the final drug product is significantly lower than the maximum reported level in the FDA Inactive Ingredient List (IIG) for ophthalmic suspension, which ensures its safe use in the final drug product under ophthalmic application.

A process for the preparation of a stable ophthalmic composition for topical administration for the treatment of ocular hypertension and glaucoma, comprising a carbonic anhydrase inhibitor, such as Brinzolamide or ophthalmologic acceptable salts thereof, as the active ingredient and an effective amount of a surfactant agent, such as Poloxamer 407 in order to provide adequate solubilization and stabilization of the low soluble active ingredient in the aqueous formulations, is provided, wherein it comprises the following steps:
- Fist forming a solution of the surfactant in water for injection;
- Then adding to the solution the total quantity of Brinzolamide;
- Autoclaving the above mixture and immediately homogenize until ambient temperature is reached;
- Passing the solution through colloidal mill to reach the desirable particle size;
- Subsequently, forming a second solution in water for injection by adding at least one tonicity agent, suspending agent, chelating agent and preservative agent and mixing until complete homogeneity;
- adjusting the pH of the second solution and autoclaving;
- Mixing the two solutions until uniform and;
- Finally, adjusting the volume with water for injection and filling in appropriate containers.

The pharmaceutical composition of the present invention may also contain one or more additional formulation ingredients selected from a wide variety of excipients. According to the desired properties of the composition, any number of ingredients may be selected, alone or in combination, based upon their known uses in preparation of stable dosage ophthalmic compositions.

Such ingredients may include, but are not limited to ophthalmologically acceptable carriers, osmotic agents, antibacterials, buffering agents, viscosity enhancing agents, tonicity, chelating and solubilizing agents. Any optional excipients must be compatible with Brinzolamide or ophthalmologically acceptable salts thereof, so that they do not interfere with the active ingredient in the composition.

Osmotic agents may be, for example, mannitol, dextrose anhydrous, dextrose hydrous, glycerin, potassium chloride, sodium chloride.
Carriers may be selected from water, water miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalylene glycols, carboxymethylcellulose, isopropyl myristate and the like.

Antibacterial agents may be selected from thimerosal, benzalconium chloride, methyl and propyl paraben, benzyl alcohol, benzyl dodecinium bromide and phenylthanol.

Buffering or pH adjusting agents may be selected form sodium hydroxide, hydrochloric acid, sodium chloride, sodium borate, sodium acetate, sodium citrate, gluconate buffers, sodium phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate potassium phosphate, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, sodium borate, potassium borate, sodium citrate, disodium citrate, sodium acetate, potassium acetate, sodium carbonate, sodium hydrogen carbonate and trometamol.

Suspending agents may be selected from carboxyvinyl polymers (Carbomers), hydroxypropyl methyl cellulose, hydroxyethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, xanthan gum, guar gum and dextrans.

Tonicity agents may be selected from sodium chloride, potassium chloride, calcium chloride, propylene glycol, glycerol, glycerin, polyethylene glycol, magnesium chloride and the like.

Chelating agents may be, for example EDTA and solubilizing agents such as Cremophor EL and tween 80.

All percentages stated herein are weight percentages based on total composition weight, unless otherwise stated.

The following examples illustrate a preferred embodiment in accordance with the present invention, without limiting the scope or the spirit of the invention.

EXAMPLES

Example 1:

TABLE 1: Qualitive & quantitative formula of compositions 1 to 5

Ingredients	**Composition 1**	**Composition 2**	**Composition 3**	**Composition 4**	**Composition 5**
	Quantity per 5ml suspension (mg)				
Mixture A					
Brinzolamide	**50.00**	**50.00**	**50.00**	**50.00**	**50.00**
Cremophor® RH40	1.25				
Cremophor® EL		1.25			
Polysorbate 80			1.25		
Poloxamer 188				1.25	
Poloxamer 407					1.25
Mixture B					
Mannitol	165.00	165.00	165.00	165.00	165.00
Sodium Chloride	12.50	12.50	12.50	12.50	12.50
Edetate disodium	0.50	0.50	0.50	0.50	0.50
Carbomer 974P	23.25	23.25	23.25	23.25	23.25
Benzalkonium Chloride solution 50% w/v	0.98	0.98	0.98	0.98	0.98
NaOH / HCl	qs to pH 7.5	qs to pH 7.5	qs to pH 7.5	qs to pH 7.5	qs to pH 7.5
water for injection (ml)	qs to 5.0ml	qs to 5.0ml	qs to 5.0ml	qs to 5.0ml	qs to 5.0ml
Total volume (ml)	**5.0ml**	**5.0ml**	**5.0ml**	**5.0ml**	**5.0ml**

Compositions 1 to 5 according to the present invention with different surfactant agent are prepared. The exact formula of the five compositions is shown in table 1.
All five compositions were prepared by using the same manufacturing process.

Initially, a first mixture is prepared by dilution of the surfactant in water and subsequently Brinzolamide is added therein. A second mixture is prepared by dissolving mannitol in water and subsequently dissolving sodium chloride, edetate sodium, carbomer 974P and benzalconium chloride therein. The pH value of the second mixture is measured and adjusted by adding the necessary amount of NaOH or HCl.
Finally, the two mixtures are homogenized together and the volume is adjusted by the necessary amount of water.

Compositions 1 to 5 were compared in terms of sedimentation volume and resuspendability as well as their chemical stability. The sedimentation volume was determined by keeping 50 ml of each suspensions in stoppered measuring cylinder and stored undisturbed at room temperature. The separation of clear liquid was noted at intervals of 5 days up to 45 days. The sedimentation volume was calculated using the formula Vu/Vo, where Vu is the volume of sediment and Vo is the original volume (50ml) of each composition tested. Values close to 1 where the sediment volume is almost equal to the original volume of each composition tested indicate a stable suspension.

TABLE 2: Sedimentation volume of compositions 1-5.

	Vu/Vo 5 days	**Vu/Vo 15 days**	**Vu/Vo 25 days**	**Vu/Vo 35 days**	**Vu/Vo 45 days**
Composition 1 (Cremophor RH-40)	0,75	0,72	0,7	0,69	0,68
Composition 2 (Cremophor EL)	0,75	0,71	0,71	0,69	0,69
Composition 3 (Polysorbate 80)	0,77	0,74	0,73	0,73	0,7
Composition 4 (Poloxamer 188)	0,96	0,93	0,91	0,9	0,89
Composition 5 (Poloxamer 407)	0,99	0,97	0,95	0,93	0,92

The results show that compositions 4 and 5 with Poloxamer are the most stable suspensions.
In order to test the resuspendability of compositions 1 to 5, accelerated settling studies were performed by subjecting 9 ml of the composition in a separate 15ml glass tube to centrifugation for 20 minutes at 1000 rpm. After centrifugation, the composition was caused to spin (40 rpm) on a rotor. The resuspendability of the settled material was tested by measuring the time required to resuspend the sediment completely (NMT 15 seconds).

TABLE 3: Resuspension time of compositions 1 to 5.

Composition	**1**	**2**	**3**	**4**	**5**
Resuspension Time (Seconds)	45	41	43	14	14

As it is shown in the table, composition 4 and 5 with Poloxamer have the best resuspendability since the resuspension time is less than 15 seconds.

Regarding the chemical stability, it is obvious that compositions 4 and 5 with Poloxamer as surfactant are the most stable after 6 months storage at 25°C/ 60% RH, 30°C/ 60% RH and 40°C/ 75% RH.

TABLE 4: Stability data of compositions 1-5 after 6 months at 25°C/ 60% RH, 30°C/ 60% RH and 40°C/ 75% RH.

Composition	**1**			**2**			**3**			**4**			**5**		
Storage temperature (°C)	**25**	**30**	**40**	**25**	**30**	**40**	**25**	**30**	**40**	**25**	**30**	**40**	**25**	**30**	**40°C**
Impurity A (NMT 1.50%)	1,06	1,58	2,12	0,80	1,59	1,91	0,98	1,78	2,17	0,48	1,06	1,23	0,46	1,01	1,21
Total Impurities (NMT 2.0%)	0,29	0,33	0,39	0,31	0,33	0,39	0,32	0,34	1,08	0,35	0,52	0,34	0,27	0,34	0,37

The physical characteristics such as pH value, osmolality, viscosity and specific gravity of all five compositions were satisfying. However, especially with regard to composition 1, 2 and 3 after 24 hours the active pharmaceutical ingredient was separated from the other ingredients and sedimentation of Brinzolamide was observed.

The use of poloxamer as a surfactant (compositions 4 & 5) significantly improved the solubilization of Brinzolamide in aqueous composition, especially the use of poloxamer 407 (composition 5) where the impurities levels are lower.

Example 2:

Composition 5 containing Poloxamer 407 as a surfactant provided satisfactory results and said composition was prepared following the same manufacturing process as stated in example 1. Steam sterilization (autoclave) has been used as the sterilization process in Composition 5.

Sterilization according to example 1 of the present invention has been performed after the final homogenization of mixtures A and B. Although physical characteristics are acceptable, degradation products have been increased over the accepted limits. Furthermore, due to the solubility of the active ingredient at autoclaving temperatures, large needle-like crystals have been formed on cooling down of the final formulation, which settle as sediment and have been difficult to be resuspended.

Composition 5 according to example 2 of the present invention has been sterilized, wherein mixture A and B have been autoclaved separately. After sterilization of mixture A, Brinzolamide has been separated from water creating a biphasic mixture. In particular, the upper phase was the water and the lower was the melted Brinzolamide which on cooling down of the mixture A converted to a compact solid mass. As a result, mixing of Mixture A and Solution B was impossible.

Accordingly, the sterilization process has been amended, wherein mixture A and mixture B of composition 5 have been autoclaved separately and immediately after sterilization, hot mixture A at temperature about 60°C – 70°C has been homogenized and added gradually to hot mixture B at temperature about 60°C – 70°C.

The physical characteristics of composition 5 thus sterilized are satisfactory and the degradation product is within accepted limits. However, some large particles have been observed which were difficult to be resuspended.

Therefore, according to example 2 the following sterilization process has been conducted to composition 5: mixture A and mixture B of composition 5 have been autoclaved separately and mixture A immediately after its sterilization has been homogenized until ambient temperature and then said mixture A has been mixed with ambient temperature mixture B, which mixture B has been homogenized, as well. Physical characteristics of composition 5 thus sterilized are satisfactory and Brinzolamide is well suspended.

Example 3

Composition 5 of example 1 using the sterilization process of example 2 has been tested in a large scale production and in order to obtain a well suspended product, mixture A passed through a colloid mill until the particle size is less than about 20 μm.

TABLE 5: Qualitive & quantitative of composition 5 according to the present invention

Ingredients	**Quantity per 5ml suspension (mg)**
Brinzolamide	**50.00**
Mannitol	165.00
Poloxamer 407	1.25
Sodium Chloride	12.50
Edetate disodium	0.50
Carbomer 974P	23.25
Benzalkonium Chloride solution 50% w/v	0.98
NaOH / HCl	qs to pH 7.5
water for injection (ml)	qs to 5.0ml
Total volume (ml)	**5.0**

Composition 5 has been prepared by using the following manufacturing process: formation of a first mixture A by diluting Poloxamer 407 in water and subsequently adding Brinzolamide therein. Mixture A is sterilized in an autoclave and then is stirred fiercely until homogeneity and ambient temperature is reached. Mixture A is transferred and passed through a colloidal mill until its particle size is less than about 20 microns.

A second mixture B is formed by dissolving Mannitol in water. Sodium chloride is added in said solution and dissolved. Then, Edetate disodium is added in the obtained mixture and dissolved. Subsequently, Carbomer 974P is added and when dissolved, Benzalkonium chloride is also added and dissolved under stirring.

Subsequently, the pH value of the obtained mixture B is being adjusted by addition of the appropriate amount of NaOH or HCl. Mixture B is also sterilized in an autoclave and stirred until homogeneity and ambient temperature is reached.

Finally, mixture A is added gradually to mixture B and mixed. The final mixture is adjusted with the necessary amount of water and the product is stored in an appropriate container.

Physical characteristics of composition 5 are satisfactory, particle size results are acceptable and stability results are adequate as presented in table 6 below.

TABLE 6: Stability data after 3 months storage at 25^0C/ 60% RH and 30^0C / 60%

Control tests	**Limits**	**Stability data after 3 months**	
		25^0C/ 60% RH	30^0C/ 60% RH
Specific Gravity	1.010-1.020g/ml	1.019	1.018
pH	pH = 7.1-7.9	7.4	7.42
Viscosity	440 ± 85cp	511	512
Osmolality	270-320 mOsmol/kg	292	288
Assay	95.0-105.0% of the stated amount of Brinzolamide	99.2%	99.0%
Benzalkonium Chloride Assay	85.0-115.0% of the stated amount of Benzalkonium Chloride	99.5%	99.1%
EDTA Assay	85.0-115.0% of the stated amount of EDTA	96.0%	97.7%
Related Substances of Brinzolamide	Methane Sulfonyl Impurity NMT 0.15%	0.08%	0.08%
	Isopropyl impurity NMT 0.15%	ND	ND
	Impurity B NMT 0.30%	0.14%	0.14%
	Any Individual Unknown NMT 0.50%,	ND	ND
	Total NMT 2.0%	0.22%	0.22%
Enantiomeric Purity	Related Compound A NMT 1.50%	0.35%	0.36%

The bioequivalence and efficacy of composition 5 according to the present invention has been tested and confirmed that all requirements have been fulfilled.

While the invention has been described with reference to various specific and preferred embodiments and examples, it should be however understood that variations and modifications may be made without departing from the spirit and scope of the invention as defined in the appended claims.

CLAIMS

1. An ophthalmic pharmaceutical composition for topical administration comprising a carbonic anhydrase inhibitor, such as Brinzolamide or ophthalmologic acceptable salts thereof, as the active ingredient and an effective amount of a surfactant, such as Poloxamer in order to provide adequate solubilization and stabilization of the low soluble active ingredient in the aqueous formulations.

2. The ophthalmic pharmaceutical composition according to claim 1, wherein the carbonic anhydrase inhibitor is Brinzolamide or ophthalmologic acceptable salts thereof.

3. The ophthalmic pharmaceutical composition according to claim 1, wherein the surfactant is Poloxamer 407.

4. The ophthalmic pharmaceutical composition according to claim 1, wherein the amount of poloxamer 407 in the composition is from about 0.01% to about 0.05% w/w.

5. The ophthalmic pharmaceutical composition according to any preceding claim, wherein it further comprises of at least one osmotic agent, a tonicity agent, a suspending agent, a chelating agent, a pH adjusting agent and a preservative.

6. The ophthalmic pharmaceutical composition according to any preceding claim, wherein it further comprises water, mannitol, benzalconium chloride, edetate disodium, sodium chloride, carbomer and sodium hydroxide or hydrochloride.

7. A process for the preparation of a stable ophthalmic composition for topical administration for the treatment of ocular hypertension and glaucoma, comprising a carbonic anhydrase inhibitor, such as Brinzolamide or ophthalmologic acceptable salts thereof, as the active ingredient and an effective amount of a surfactant agent, such as Poloxamer 407 in order to provides adequate solubilization and stabilization of the low soluble active ingredient in the aqueous formulations, wherein it comprises the following steps:
   - Fist forming a solution of the surfactant in water for injection;
   - Then adding to the solution the total quantity of Brinzolamide;
   - Autoclaving the above mixture and subsequently homogenize until ambient temperature is reached;
   - Passing the obtained solution through colloidal mill to reach the desired particle size;
   - Subsequently, forming a second solution in water for injection by adding at least one osmotic agent, a tonicity agent, a suspending agent, a chelating agent and a preservative agent and mixing until complete homogeneity;
   - adjusting the pH of the second solution by adding NaOH or HCL;
   - autoclaving the obtained solution and subsequently homogenize until ambient temperature is reached;
   - Mixing gradually the two formed solutions until uniform, and
   - Finally, adjusting the final mixture with water for injection and filling in appropriate container.

8. The process according to claim 7, wherein the surfactant is poloxamer 407.

9. The process according to claim 7, wherein the amount of poloxamer 407 in the composition is from about 0.01% to about 0.05% w/w.

10. The process according to claim 7, wherein the composition further comprises mannitol, benzalconium chloride, edetate disodium, sodium chloride, carbomer and sodium hydroxide or hydrochloride.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/000697

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/08
ADD.

According to International Patent Classification (IPC) or to 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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/25620 A1 (ALCON LAB INC [US]) 18 June 1998 (1998-06-18) cited in the application claim 1; example 4	1-10
X	US 2006/257487 A1 (OWEN GEOFFREY R [US] ET AL) 16 November 2006 (2006-11-16) example 5; table 3	1-6
X,P	WO 2013/025696 A1 (TEVA PHARMA [IL]; TEVA PHARMA [US]; CETINA-CIZMEK BISERKA [HR]; BRACKO) 21 February 2013 (2013-02-21) page 32; example 3	1-6

☐ 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

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1

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