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(54) Title: METHOD FOR STABILIZING PHARMACEUTICAL COMPOSITIONS BY SPECIAL USE OF AN ANTIOXIDANT		
(57) Abstract The present invention describes in particular a method for stabilizing a pharmaceutical composition by contacting said composition with a polymeric material comprising an antioxidant.		

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METHOD FOR STABILIZING PHARMACEUTICAL COMPOSITIONS BY SPECIAL USE OF AN ANTIOXIDANT

The present invention describes in particular a method for stabilizing a pharmaceutical composition by contacting said composition with a polymeric material comprising an antioxidant.

There exists a need to stabilize pharmaceutical compositions, in particular aqueous pharmaceutical compositions and in particular aqueous eye drops, such that they are stable against decomposition caused by heat, light and/or oxygen exposure.

The problem has been solved in accordance to the main claim, namely in particular by the use of a plastic bottle, wherein an antioxidant is comprised. The advantage of such a stabilization consists in the possibility to omit an additional antioxidant and/or a stabilizer otherwise needed in such pharmaceutical compositions. Therefore, such pharmaceutical compositions usually exhibit an enhanced tolerability as compared to ordinarily stabilized compositions, since the antioxidant is not administered to the organism in need of such a pharmaceutical composition.

Consequently, an object of the present invention is a method of stabilizing a pharmaceutical composition in particular in accordance to the main claim, e.g. by use of a plastic bottle comprising an antioxidant.

Within the present invention stabilization relates to the stability of the pharmaceutical composition in total and in particular to the stability of the active ingredient itself when exposed to storage, oxygen and/or air (oxygen radicals), light (UV) and/or heat (e.g. sterilization step at 121°C). Heat sterilization will equally refer to autoclavation.

The term polymeric material relates to a polymer which is preferably insoluble in the liquid pharmaceutical composition of the present invention and which polymeric material may further be in the form of a random mold. Examples of molds are in particular a pellet, a bead, a rod, a bar, a sheet, a tube, or a vessel and more preferably a bottle. A preferred polymeric material comprises or consists of polyethylene (PE), polypropylene (PP) and/or mixtures thereof.

Consequently, the term plastic bottle relates in particular to a polyethylene (PE) and/or a polypropylene (PP) bottle. These may optionally contain further auxiliaries such as a light absorbing material e.g. titanium dioxide, a color pigment, a UV-absorber and/or the like.

An antioxidant within the terms of the present invention is understood to be a compound selected from the group consisting of 2,2',2'',6,6',6''-Hexa-(1,1-dimethylethyl)-4,4',4''-[(2,4,6-trimethyl-1,3,5-benzenetriyl)-trismethylene]-triphenol (Irganox 1330), 1,3,5,tris[3,5-di(1,1-dimethylethyl)-4-hydroxybenzyl]-1H,3H,5H-1,3,5-triazine-2,4,6-trione, pentaerythrityl tetrakis[3-[3,5-di(1,1-dimethylethyl)-4-hydroxyphenyl]-propionate], octadecyl-3-[3,5-di(1,1-dimethylethyl)-4-hydroxyphenyl]-propionate, tris[2,4-di(1,1-dimethylethyl)-phenyl]-phosphite, 2,2'-di(octa-decyloxy)-5,5'-spirobi(1,3,2-dioxaphosphorinane), dioctadecyl disulphide, didodecyl-3,3'-thiodipropionate, dioctadecyl-3,3'-thiodipropionate, butylhydroxytoluene, ethylene bis[3,3-di[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butyrate] and mixtures thereof. A preferred antioxidant is Irganox 1330.

The amount of antioxidant comprised in the polymeric material is typically in the range of the recommendations of the European Pharmacopoeia and is typically from 0.05 - 1.0 wt.%, more preferably from 0.1 - 0.7 wt.% and even more preferably from 0.12 - 0.55 wt. %.

Other antioxidants, such as ascorbic acid, acetylcysteine, cysteine, sodium hydrogen sulfite, butyl-hydroxyanisole, and alpha-tocopherol acetate may be present too.

An advantage of an antioxidant comprised in a polymeric material in accordance to the present invention is that there is typically only a minimal release or substantially no release of said antioxidant into a pharmaceutical and in particular into an aqueous ophthalmic composition which composition is in contact with said polymeric material. This may typically result in a substantial exclusion of said antioxidant from said pharmaceutical composition.

An antioxidant is typically used during the manufacturing process of a polymeric material in order to avoid decomposition and/or oxidation. Consequently, such a polymer is in particular within the terms of the present invention, namely a polymeric material comprising an antioxidant.

A pharmaceutical active ingredient is e.g. selected from the group consisting of acetylcholine chloride, acyclovir, adrenaline, amethocaine, aminocaproic acid, antazoline phosphate, arachidonic acid, atropine, betaxolol, bupivacaine, carbachol, carteolol, chloramphenicol, chlortetracycline, chymotrypsin, clonidine, cocaine, corynanthine, cromolyn, cyclopentolate, demecarium, dexamethasone, dibutoline, dichlorphenamide, diclofenac, dipivefrin, echodtiophate, ephedrine, erythromycin, ethambutol, etidocaine, eucatropine, fluoromethalone, fluorometholone, gentamycin, gramicidine, H-thymidine, homatropine, hyaluronic acid, hydrocortisone, idoxuridine, indomethacin, isofluorophate, isosorbide, ketorolac, ketotifen, lachesine, levobunolol, levocabastine, lidocaine, lignocaine, medrysone, mepivacaine, methacholine, methazolamide, naphazoline, natamycin, neomycin, neostigmine, noradrenaline, ofloxacin, oxybuprocaine, oxymetazolin, oxyphenonium, pheniramine, phenylephrine, physostigmine, pilocarpine, polymyxin B, prednisolone, proparacaine, proxymethacaine, pyrilamine, retinoic acid, retinol, retinol acetate, retinol palmitate, scopolamine, sorbinil, sulfacetamide, tamoxifen, tetracaine, tetracycline, tetrahydrozoline, timolol, trifluridine, tropicamide, vidarabine, and pharmaceutically acceptable salts, and mixtures thereof.

Preferred pharmaceutically active compounds are selected from the group of betaxolol, chloramphenicol, diclofenac, dipivefrin, ephedrine, erythromycin, gentamycin, indomethacin, ketotifen, levobunolol, levocabastine, ofloxacin, pilocarpine, polymyxin B, prednisolone, retinoic acid, retinol, retinol acetate, retinol palmitate, tetracycline and pharmaceutically acceptable salts thereof.

More preferred pharmaceutically active compounds are selected from the group of, betaxolol, chloramphenicol, diclofenac, ketotifen, levobunolol, levocabastine, pilocarpine, retinoic acid, retinol, retinol acetate, retinol palmitate and pharmaceutically acceptable salts thereof.

Highly preferred is ketotifen, retinoic acid, retinol, retinol acetate, retinol palmitate and pharmaceutically acceptable salts thereof.

Very particular preferred is ketotifen and pharmaceutically acceptable salts thereof.

Within the present invention a pharmaceutical composition is characterized by the carrier wherein said pharmaceutical active compound is mixed, suspended, dissolved and/or

partially dissolved and is selected from the group consisting of water, mixtures of water and water-miscible solvents, such as C₁- to C₇-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% by weight hydroxyethylcellulose, ethyl oleate, carboxymethyl-cellulose, polyvinyl-pyrrolidone and other non-toxic water-soluble polymers, in particular for ophthalmic uses, such as, for example, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxy-methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropyl-cellulose and hydroxypropylcellulose, acrylates or methacrylates, such as salts of polyacrylic acid or ethyl acrylate, polyacrylamides, natural products, such as gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar and acacia, starch derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products, such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably cross-linked polyacrylic acid, such as neutral Carbopol, or mixtures of those polymers. Preferred carriers are water, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropylcellulose and hydroxypropylcellulose, neutral Carbopol, or mixtures thereof. A highly preferred carrier is water. The concentration of the carrier is, typically, from 1 to 100000 times the concentration of the active ingredient. The term aqueous typically denotes an aqueous composition wherein the carrier is to an extent of >50%, more preferably >75% and in particular >90% by weight water.

Within the terms of the present invention the term composition relates in particular to a solution, a suspension, a gel, an ointment, an emulsion and/or a mixture thereof.

Further preference is given to pharmaceutical compositions which are suitable for ocular administration. Therefore such a pharmaceutical composition preferably comprises further ingredients in order to meet the prerequisites for ocular tolerability. In a particular aspect, the present invention relates therefore to the stabilization of an ophthalmic composition and in particular to an aqueous ophthalmic composition.

These further ingredients may include tonicity enhancers, preservatives and pH adjusting agents.

For the adjustment of the pH, preferably to a physiological pH, buffers may especially be useful. Examples of buffer substances are acetate, ascorbate, borate, hydrogen carbonate

/carbonate, citrate, gluconate, lactate, phosphate, propionate and TRIS (tromethamine) buffers. Tromethamine and borate buffer are preferred buffers. The amount of buffer substance added is, typically, that necessary to ensure and maintain a physiologically tolerable pH range. The pH range is generally in the range of from 4 to 9, preferably from 4.5 to 8.5 and more preferably from 5.0 to 8.2.

Tonicity is adjusted if needed typically by tonicity enhancing agents. Such agents may, for example be of ionic and/or non-ionic type. Examples of ionic tonicity enhancers are e.g. alkali metal or earth metal halides, such as, for example, CaCl_2 , KBr, KCl, LiCl, NaI, NaBr or NaCl, Na_2SO_4 or boric acid. Non-ionic tonicity enhancing agents are, for example, urea, glycerol, sorbitol, mannitol, propylene glycol, or dextrose. Typically, a sufficient amount of tonicity enhancing agent may be added to impart to an above ophthalmic composition an osmolality of approximately from 50 to 1000 mOsmol, preferred from 100 to 400 mOsmol, more preferred from 200 to 400 mOsmol and even more preferred from 250 to 350 mOsmol.

A preservative may typically be selected from a quaternary ammonium compound such as benzalkonium chloride, benzoxonium chloride or the like. Benzalkonium chloride is better described as: N-benzyl-N-(C_8 - C_{18} alkyl)-N,N-dimethylammonium chloride. Examples of preservatives different from quaternary ammonium salts are alkyl-mercury salts of thiosalicylic acid, such as, for example, thiomersal, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate, parabens, such as, for example, methylparaben or propylparaben, alcohols, such as, for example, chlorobutanol, benzyl alcohol or phenyl ethanol, guanidine derivatives, such as, for example, chlorohexidine or polyhexamethylene biguanide, sodium perborate, Germal®II or sorbic acid. Preferred preservatives are quaternary ammonium compounds, in particular benzalkonium chloride, alkyl-mercury salts and parabens. Where appropriate, a sufficient amount of preservative is added to the ophthalmic composition to ensure protection against secondary contaminations during use caused by bacteria and fungi.

A pharmaceutical composition may additionally require the presence of a solubilizer, in particular if the active or the inactive ingredients tends to form a suspension or an emulsion. A solubilizer suitable for an above concerned composition is for example selected from the group consisting of tyloxapol, fatty acid glycerol polyethylene glycol esters, fatty acid

polyethylene glycol esters, polyethylene glycols, glycerol ethers, a cyclodextrin (for example α -, β - or γ -cyclodextrin, e.g. alkylated, hydroxyalkylated, carboxyalkylated or alkyloxycarbonyl-alkylated derivatives, or mono- or diglycosyl- α -, β - or γ - cyclodextrin, mono- or dimaltosyl- α -, β - or γ - cyclodextrin or panosyl-cyclodextrin), polysorbate 20, polysorbate 80 or mixtures of those compounds. A specific example of an especially preferred solubilizer is a reaction product of castor oil and ethylene oxide, for example the commercial products Cremophor EL[®] or Cremophor RH 40[®]. Reaction products of castor oil and ethylene oxide have proved to be particularly good solubilizers that are tolerated extremely well by the eye. Another preferred solubilizer is selected from tyloxapol and from a cyclodextrin. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient. For example, the concentration of the solubilizer is from 0.1 to 5000 times the concentration of the active ingredient.

An above pharmaceutical composition may comprise further non-toxic excipients, such as, for example, emulsifiers, wetting agents or fillers, such as, for example, the polyethylene glycols designated 200, 300, 400 and 600, or Carbowax designated 1000, 1500, 4000, 6000 and 10000. Other excipients that may be used if desired are listed below but they are not intended to limit in any way the scope of the possible excipients. The amount and type of excipient added is in accordance with the particular requirements and is generally in the range of from approximately 0.0001 to approximately 90% by weight.

Further objects of the present invention are those disclosed in all dependent and independent claims.

A further object of the present invention is the use of a plastic bottle in accordance to the examples for stabilizing a composition disclosed therein.

Example 1: Ketotifen 0.025% Eye Drops

	in 10 ml PE-bottles (no antioxidant)	in 10 ml PP-bottles (+ Irganox 1330)
0 - Value		
Content of ketotifen hydrogen fumarate in %	97.7	97.7
pH	5.06	5.06
Osmolality (mOsmol)	247	247
Stresstest, 15 hrs, 80°C		
Content of ketotifen hydrogen fumarate in %	73.7	96.2
Known degradation products in %	2.6	0.04
pH	4.42	4.96
Osmolality (mOsmol)	247	248

Example 2: Ketotifen 0.05% Eye Drops

	10 ml PE-bottles (white) (no antioxidant)	10 ml PP-bottles (white) (+ Irganox 1330)
0-Value		
Content of ketotifen hydrogen fumarate in %	97.8	97.8
pH	5.30	5.30
Osmolality (mOsmol)	248	248
3 month, 25°C		
Content of ketotifen hydrogen fumarate in %	96.0	99.2
Known degradation products in %	0.6	not detectable
Unknown degradation products in %	not determinable	not detectable
pH	5.0	5.64
3 month, 30°C		
Content of ketotifen hydrogen fumarate in %	93.5	99.2
Known degradation products in %	1.6	not detectable
Unknown degradation products in %	0.5	not detectable
pH	4.93	5.62

3 month, 40°C (20% relative humidity)		
Content of ketotifen hydrogen fumarate in %	79.2	99.8
Known degradation products in %	7.5	not determinable
Unknown degradation products in %	3.2	not detectable
pH	4.57	5.35
3 month, 40°C (75% relative humidity)		
Content of ketotifen hydrogen fumarate in %	83.4	99.4
Known degradation products in %	4.3	not detectable
Unknown degradation products in %	1.6	not detectable
pH	4.66	5.55

Example 3:

Ingredients comprised in a 0.025% ophthalmic composition comprising ketotifen:

Names of ingredients	(mg/ml)	Function	Reference to standards
Active ingredient			
Ketotifen (used as Ketotifen hydrogen fumarate)	0.25 (0.345)	antiallergic agent	
Other ingredients			
Benzalkonium chloride	0.10	preservative	Ph. Eur.
Glycerol	21.25	isotonizing agent	Ph. Eur.
1 M Sodium hydroxide	~0.75 (to a pH of about 5.3)	pH adjusting agent	Ph. Eur.
Water for injections	~981.055 (ad 1.0 ml)	solvent	Ph. Eur.

Example 4:

Ingredients comprised in a 0.05% ophthalmic composition comprising ketotifen:

Names of ingredients	Formula (mg/ml)	Function	Reference to standards
Active ingredient			
Ketotifen (used as Ketotifen hydrogen fumarate)	0.50 (0.69)	antiallergic agent	
Other ingredients			
Benzalkonium chloride	0.10	preservative	Ph. Eur.
Glycerol 85 %	25.00	tonicity adjusting agent	Ph. Eur.
Sodium hydroxide 1 N	~1.50 (to a pH of about 5.3)	pH adjusting agent	Ph. Eur.
Water for injections	~976.21 (ad 1.0 ml)	solvent	Ph. Eur.

Example 5:

Vitamin A eye drops

	5 ml PE-bottles without antioxidant	5 ml PP-bottles with Irganox 1330
0-Value		
Content of Vit. A palmitate in IU	1272	1272
pH	6.67	6.67
Osmolality (mOsmol)	310	310
40°C, 1 month, 75% relative humidity		
Content of Vit. A palmitate in IU	1097	1204
pH	6.67	6.67
Osmolality (mOsmol)	310	310

Example 6:

Ingredients comprised in Vitamin A eye drops (gel)

compound	mg/ml	function	reference to standards
synthetic vitamin A palmitate, water dispersible form (100'000 IU/g)	10 (1000 IU)	antixerophthalmic	Ph. Eur.
benzalkonium chloride	0.10	preservative	Ph. Eur.
α -tocopherol acetate, water dispersible form (0.5 g/g)	10.0	antioxidant	
boric acid	16.20	buffer	Ph. Eur.
borax	1.40	buffer	Ph. Eur.
disodium edetate	1.00	chelating agent	Ph. Eur.
methylhydroxypropylcellulose	4.00	viscosity enhancer	Ph. Eur.
water for injections	ad 1.0 ml	carrier (solvent)	Ph. Eur.

Ph. Eur. = European Pharmacopoeia

IU = International Units

Example 7

Ketotifen eye drops of example 3 (0.025% ophthalmic composition) exposed to stability test:

Composition (mg/ml)	Batch-7A filled into PP-bottles containing Irganox 1330,	Batch-7B filled into PP-bottles containing Irganox 1330, autoclaved before filling	Batch-7C PP-bottles containing BHT, sterilised with ethylene oxide before filling
ketotifen hydrogen fumarate	0.345	identical to 7A	identical to 7A
benzalkonium chloride	0.10	identical to 7A	identical to 7A
glycerol	21.25	identical to 7A	identical to 7A
1 M sodium hydroxide	~0.75	identical to 7A	identical to 7A
Water for injection	~981.055	identical to 7A	identical to 7A

O-Value

Content of ketotifen hydrogen fumarate in %	96.5	100.0	99.6
pH	5.12	5.38	5.55
osmolality (mOsmol)	241	238	238

stress test at 40°C and 75% relative humidity

	12 months	3 months	3 months
Content of ketotifen hydrogen fumarate in %	99.9	99.2	98.2
degradation products in %	~2.08	<0.1	<0.05
pH	5.16	5.35	5.56
Osmolality (mOsmol)	244	240	242

BHT: butylhydroxytoluene

Claims

1. Method for the stabilization of a pharmaceutical composition characterized by contacting said composition with a polymeric material comprising an antioxidant, which polymeric material is insoluble in said pharmaceutical composition.
2. Method of claim 1, wherein said pharmaceutical composition is an aqueous composition.
3. Method of claim 1, wherein said pharmaceutical composition is an aqueous ophthalmic composition.
4. Method of claim 1 - 3, wherein said composition is a solution, suspension or gel, and preferably a solution.
5. Method of claim 1, wherein said polymeric material is selected from polyethylene, polypropylene and a mixture thereof, and preferably polypropylene.
6. Method of claim 5, wherein said polymeric material is a mold, in particular a pellet, a bead, a rod, a bar, a sheet, a tube, or a vessel and more preferably a bottle.
7. Method of claim 1, wherein said antioxidant is selected from the group consisting of 2,2',2'',6,6',6''-Hexa-(1,1-dimethylethyl)-4,4',4''-[(2,4,6-trimethyl-1,3,5-benzenetriyl)-trimethylene]-triphenol (Irganox 1330), 1,3,5,tris[3,5-di(1,1-dimethylethyl)-4-hydroxybenzyl]-1H,3H,5H-1,3,5-triazine-2,4,6-trione, pentaerythrityl tetrakis[3-[3,5-di(1,1-dimethylethyl)-4-hydroxyphenyl]-propionate], octadecyl-3-[3,5-di(1,1-dimethylethyl)-4-hydroxyphenyl]-propionate, tris[2,4-di(1,1-dimethylethyl)-phenyl]-phosphite, 2,2'-di(octa-decyloxy)-5,5'-spirobi(1,3,2-dioxaphosphorinane), dioctadecyl disulphide, didodecyl-3,3'-thiodipropionate, dioctadecyl-3,3'-thiodipropionate, butylhydroxytoluene, ethylene bis[3,3-di[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butyrate] and mixtures thereof.
8. Method of claim 1 or claim 6, wherein said polymeric material is selected from polypropylene and polyethylene and said antioxidant is selected from the group consisting of 2,2',2'',6,6',6''-Hexa-(1,1-dimethylethyl)-4,4',4''-[(2,4,6-trimethyl-1,3,5-benzenetriyl)-trimethylene]-triphenol (Irganox 1330), 1,3,5,tris[3,5-di(1,1-dimethylethyl)-4-hydroxybenzyl]-

1H,3H,5H-1,3,5-triazine-2,4,6-trione, pentaerythrityl tetrakis[3-[3,5-di(1,1-dimethylethyl)-4-hydroxyphenyl]-propionate], octadecyl-3-[3,5-di(1,1-dimethylethyl)-4-hydroxyphenyl]-propionate and tris[2,4-di(1,1-dimethylethyl)-phenyl]-phosphite, 2,2'-di(octa-decyloxy)-5,5'-spirobi(1,3,2-dioxaphosphorinane).

9. Method of claim 1 or 6, wherein said polymeric material is polypropylene and said antioxidant is selected from butylhydroxytoluene and preferably from 2,2',2'',6,6',6''-Hexa-(1,1-dimethylethyl)-4,4',4''-[(2,4,6-trimethyl-1,3,5-benzenetriyl)-trismethylene]-triphenol (Irganox 1330).

10. Method of claim 1, wherein said composition is an ophthalmic composition, said polymeric material is polypropylene and said antioxidant is selected from 2,2',2'',6,6',6''-Hexa-(1,1-dimethylethyl)-4,4',4''-[(2,4,6-trimethyl-1,3,5-benzenetriyl)-trismethylene]-triphenol (Irganox 1330) and preferably from butylhydroxytoluene.

11. Method of claim 10, wherein said ophthalmic composition further comprising a pharmaceutically active ingredient selected from the group consisting of ketotifen, retinoic acid, retinol, retinol acetate, retinol palmitate and pharmaceutically acceptable salts thereof.

12. Method of claim 10, wherein said composition further comprises a buffer, a tonicity enhancer and in particular a preservative.

13. Use of an antioxidant which is incorporated into a polymeric material for the stabilization of a pharmaceutical and in particular an ophthalmic composition.

14. Use of claim 13, wherein said composition further comprises a pharmaceutically active ingredient selected from the group consisting of ketotifen, retinoic acid, retinol, retinol acetate, retinol palmitate and pharmaceutically acceptable salts thereof.

15. An aqueous ophthalmic composition comprising ketotifen or a pharmaceutically acceptable salt thereof and an antioxidant incorporated into a polymeric material, which polymeric material is selected from the group consisting of polyethylene, polypropylene or a mixture thereof.

16. Composition of claim 15, wherein said antioxidant is selected from the group consisting of 2,2',2'',6,6',6''-Hexa-(1,1-dimethylethyl)-4,4',4''-[(2,4,6-trimethyl-1,3,5-benzenetriyl)-trimethylene]-triphenol (Irganox 1330), 1,3,5, tris[3,5-di(1,1-dimethylethyl)-4-hydroxybenzyl]-1H,3H,5H-1,3,5-triazine-2,4,6-trione, pentaerythrityl tetrakis[3-[3,5-di(1,1-dimethylethyl)-4-hydroxyphenyl]-propionate], octadecyl-3-[3,5-di(1,1-dimethylethyl)-4-hydroxyphenyl]-propionate, tris[2,4-di(1,1-dimethylethyl)-phenyl]-phosphite, 2,2'-di(octa-decyloxy)-5,5'-spirobi(1,3,2-dioxaphosphorinane), dioctadecyl disulphide, didodecyl-3,3'-thiodipropionate, dioctadecyl-3,3'-thiodipropionate, butylhydroxytoluene, ethylene bis[3,3-di[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butyrate] and mixtures thereof, and preferably wherein said antioxidant is Irganox 1330.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/445 A61K47/10 A61K47/32

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)

IPC 6 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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 096, no. 010, 31 October 1996 (1996-10-31) & JP 08 165240 A (HISAMITSU PHARMACEUT CO INC), 25 June 1996 (1996-06-25)	1-14
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Y	*cf. abstract, col. 3, lines 50-57 and col. 4, first line, col. 6, lines 19-30*	15, 16
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

5 August 1999

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/02221

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 4 959 208 A (DENISON JOHN M ET AL) 25 September 1990 (1990-09-25)	1-14
Y	*cf. col. 1, lines 8-13, lines 58-65, col. 14, lines 35-40 and table 1 on col. 14 bridging with col. 15* -----	15,16

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information on patent family members

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