

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

07 March 2019 (07.03.2019)



(10) International Publication Number

WO 2019/043723 A1

(51) International Patent Classification:

A61K 36/00 (2006.01) A61K 31/355 (2006.01)
A61K 9/10 (2006.01) A61K 47/10 (2017.01)

Published:

- with international search report (Art. 21(3))
- in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE

(21) International Application Number:

PCT/IN2018/050170

(22) International Filing Date:

26 March 2018 (26.03.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

201741030659 30 August 2017 (30.08.2017) IN

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

(54) Title: EMULSIONS FOR OPHTHALMIC DELIVERY OF ANTIOXIDANTS

(57) Abstract: A ophthalmic emulsion for ocular delivery of antioxidants comprising one or more antioxidants, at least one oil of vegetable, mineral or animal origin, at least one surfactant and at least one pharmaceutically acceptable excipient, wherein the pH is in the range of about 4 to 8.



EMULSIONS FOR OPHTHALMIC DELIVERY OF ANTIOXIDANTS

FIELD OF THE INVENTION

This invention relates to drug delivery dosage forms and methods to treat medical conditions of the eye. Specifically, this invention relates to emulsion drug delivery dosage forms of antioxidants for drug delivery within the eye.

BACKGROUND

Age related macular degeneration (ARMD) is a severe problem of the eye which accounts for the loss of vision of huge number of elderly population across the globe. The disease which starts as a mild innocent problem of the eye, including occasional floaters and black dots in front of the eye gradually progresses to the loss of peripheral vision to complete loss of vision

Antioxidants are well known to slow down the progression of the ARMD disease. There are several formulations available in the market containing single or combination of antioxidants like Alpha Tocopherol, Lutein, Zeaxanthin, Beta Carotene, Selenium, etc for oral administration for slowing down the progression of the disease. There are several drawbacks with orally administered drugs or bioactives as the drug does not reach the eye at appropriate concentrations and has either none or very poor pharmacological action in the eye when administered through oral route.

Hence, there is a need for a topical formulation of antioxidants for ocular administration that will release the drug in a sustained manner in the eye which on repeated administration will lead to a steady concentration of antioxidants in the aqueous and vitreous humor thereby increasing the macular pigment optical density

(MPOD), which will be helpful for better management of Age Related Macular Degeneration.

SUMMARY

Accordingly, the invention provides new topical drug delivery system that releases the active agent in a sustain manner to provide the desired therapeutic effects, and methods of making such systems. The topical drug delivery system of the invention as disclosed herein is an emulsion. The emulsion composition as disclosed herein provides release of the active agent in sustained manner and repeated administration of the formulation several times a day will lead to a steady concentration of antioxidants in the aqueous & vitreous humor increasing the macular pigment optical density (MPOD), which will be helpful for better management of Age Related Macular Degeneration.

The emulsion composition as disclosed herein is a stable oil-in-water ophthalmic emulsion comprising one or more antioxidants, at least one oil from vegetable, mineral or animal origin, at least one surfactant and at least one pharmaceutically acceptable excipient, wherein the pH range is from about 4 to 8. The concentration of the antioxidant in the emulsion composition as disclosed herein is in the range of about 0.0003%-0.3% w/v and the antioxidant is selected from the group comprising of lutein, zeaxanthin, tocopherol, beta carotene, selenium or a combination thereof.

The oil is a vegetable oil or mineral oil or animal oil or a combination thereof. The vegetable oil is selected from the group comprising of Castor Oil, Cotton seed Oil, Peanut Oil, Coconut oil, Rice bran oil, Sunflower oil, Sesame oil, Soyabean oil, Flax oil, Canola oil, Olive oil, Mustard Oil, Jojoba oil or a combination thereof. The animal oil is selected from the group comprising of fish oil, shark liver oil, cod liver oil or a combination thereof. The mineral oil is Liquid Paraffin, .

The surfactant is selected from the group comprising of Polyoxyethylated nonionic surfactants like Polysorbate80, Polysorbate 60, Polysorbate, 40, Polysorbate 20, Cremophors, Tyloxapols, Poloxamers, Benzalkonium chloride, Benzethonium chloride, Cetyl alcohol, Carbomer, Cholesterol, Cocamidopropyl betaine, glyceryl monostearate, lanolin alcohols, lauralkonium chlorides, N lauroylsarcosine, Nonoxynol 9, Octoxynol 40, Polyoxyl 35 castor oil, Polyoxyl 40 hydrogenated castor oil, Polyoxyl 40 stearate, Sorbitanmonolaureate, Sorbitan monooleate, Sorbitanmonopalmitate, Polyoxyethylene (2) Steryl Ether, Polyoxyethylene (2) Cetyl Ether, Polyoxyethylene (2) Oleyl Ether, Polyeoxyethylene (2) Nonylphenylether, Polyoxyethylene (2) isooctylphenyl ether, Polyoxyletheylene (4) lauryl ether, Polyoxyletheylene (5) isooctylphenylether or a combination thereof.

The emulsion composition as described herein further comprises at least one pH adjusting agent, at least one buffering agent, at least one osmolarity control agent and at least one antimicrobial preservative.

The pH adjusting agent selected from the group comprising of Hydrochloric Acid, Sodium Hydroxide, Sulphuric Acid, Sodium Sulphate, Acetic Acid, Sodium Citrate, Ammonium Hydroxide, Citric Acid, Diethanolamine, Nitric Acid, Phosphoric Acid or a combination thereof.

The buffering agent selected from the group comprising of Acetic Acid, Boric Acid, Citric Acid, Phosphoric Acid, Potassium Acetate, Potassium Phosphate, Potassium Sulphate, Potassium Sorbate, Sodium Acetate, Sodium borate, Sodium Carbomate, Sodium Citrate, Sodium Phosphate, Sorbic Acid, Tromethamine or a combination thereof.

The osmolarity control agent selected from the group comprising of Sodium Chloride, Sodium Sulphate, Sodium Nitrate, Sorbitol, Mannitol, Calcium Chloride,

Glycerine, Magnesium Chloride, PEG 300, PEG 400, Potassium Chloride, Propylene Glycol or a combination thereof.

The antimicrobial preservative selected from the group comprising of Quaternary ammonium compounds selected from Benzalkonium Chloride, Benzethonium chloride, Benzododecinium bromide or Polyquaternium-1; or Acid/Base compounds selected from Boric acid, sodium acetate or sodium borate; or Alcohols selected from chlorobutanol or Phenylethyl alcohol; or Organic Mercuric compounds selected from Phenyl mercuric acetate, Phenyl mercuric nitrate or Thimerosal; or Parabens selected from methyl paraben or Propyl Paraben; or Oxidizing agent sodium chlorite; or Metal salt Zinc Chloride or a combination thereof.

DETAILED DESCRIPTION

As described herein, the disclosure provides emulsion compositions for ocular delivery of antioxidants that releases the active agent in sustained manner and repeated administration of the formulation several times a day will lead to a steady concentration of antioxidants in the aqueous and vitreous humor increasing the macular pigment optical density (MPOD), which will be helpful for better management of Age Related Macular Degeneration.

The emulsion composition as disclosed herein is a stable oil-in-water ophthalmic emulsion comprising one or more antioxidants, at least one oil from vegetable, mineral or animal origin, at least one surfactant and at least one pharmaceutically acceptable excipient, wherein the pH range is from about 4 to 8.

The antioxidant is selected from the group comprising of lutein, zeaxanthin, tocopherol, beta carotene, selenium or a combination thereof. The concentration of

the antioxidant in the emulsion composition as disclosed herein is in the range of about 0.0003%-0.3% w/v.

The emulsion composition as described herein further comprises at least one pH adjusting agent, at least one buffering agent, at least one osmolarity control agent and at least one antimicrobial preservative.

The oil is a vegetable oil or mineral oil or animal oil or a combination thereof. The vegetable oil is selected from the group comprising of Castor Oil, Cotton seed Oil, Peanut Oil, Coconut oil, Rice bran oil, Sunflower oil, Sesame oil, Soyabean oil, Flax oil, Canola oil, Olive oil, Mustard Oil, Jojoba oil or a combination thereof. The animal oil is selected from the group comprising of fish oil, shark liver oil, cod liver oil or a combination thereof. The mineral oil is Liquid Paraffin.

The surfactant is selected from the group comprising of Polyoxyethylated nonionic surfactants like Polysorbate80, Polysorbate 60, Polysorbate, 40, Polysorbate 20, Cremophors, Tyloxapols, Poloxamers, Benzalkonium chloride, Benzethonium chloride, Cetyl alcohol, Carbomer, Cholesterol, Cocamidopropyl betaine, glyceryl monostearate, lanolin alcohols, lauralkonium chlorides, N lauroylsarcosine, Nonoxynol 9, Octoxynol 40, Polyoxyl 35 castor oil, Polyoxyl 40 hydrogenated castor oil, Polyoxyl 40 stearate, Sorbitanmonolaureate, Sorbitan monooleate, Sorbitanmonopalmitate, Polyoxyethylene (2) Steryl Ether, Polyoxyethylene (2) Cetyl Ether, Polyoxyethylene (2) Oleyl Ether, Polyoxyethylene (2) Nonylphenylether, Polyoxyethylene (2) isooctylphenyl ether, Polyoxyethylene (4) lauryl ether, Polyoxyethylene (5) isooctylphenylether or a combination thereof.

In one embodiment, the topical ocular suspension comprises the antioxidants lutein and zeaxanthin and pharmaceutical excipients.

Example: 1

Lutein + Zeaxanthin Ophthalmic Emulsion

S. No	Ingredient	mg/mL
1	Lutein	3 mg
2	Zeaxanthin	3 mg
3	Seasame Oil	36 mg
4	Polysorbate 80	24 mg
5	Hydroxypropyl Methyl Cellulose (HPMC)	10 mg
6	Benzalkonium Chloride	1 mg
7	Water for Injection	q.s
8	Sodium citrate	20 mg
9	Hydrochloric acid/ sodium hydroxide	q.s

Process: Sesame oil was heated to about 70° C and to it was added Lutein & Zeaxanthin and stirred to completely dissolve the same in the oil phase. Sterile purified water was heated to about 70° C, and to it polysorbate 80, Sodium citrate, Benzalkonium Chloride and HPMC was added and mixed to form the aqueous phase. The oil phase was added while stirring the aqueous phase with a high shear mixer to form the emulsion. This crude emulsion was finely divided in a high pressure homogenizer and the volume was made up with sufficient quantity of water for injection and the pH was adjusted using either sodium hydroxide/ hydrochloric acid and sterilized by filtration through 0.22 µm membrane filter to form the sterile ophthalmic emulsion of antioxidants, which is filled into containers aseptically and sealed.

In another embodiment, the ophthalmic emulsion comprises the antioxidants lutein, zeaxanthin, alpha tocopherol, and selenium and pharmaceutical excipients.

Example: 2

Lutein , Zeaxanthin, Alpha Tocopherol & Selenium Ophthalmic Emulsion

S. No	Ingredient	mg/mL
1	Lutein	3mg
2	Zeaxanthin	6mg
3	Alpha Tocopherol	0.5 mg
4	Selenium	0.01 mg
5	Peanut Oil	81 mg
6	Poloxamer 188	56 mg
7	Polyethylene Glycol (PEG) 400	20 mg
8	Sodium chloride	9 mg
9	Phenyl mercuric nitrate	2 mg
10	Water for Injection	q.s
11	Sodium Hydroxide/Hydrochloric Acid	q.s

Process: Peanut oil was heated to about 70° C and to it was added Lutein, Zeaxanthin and alpha tocopherol and stirred to completely dissolve the same in the oil phase. Sterile purified water was heated to about 70° C ,and to it Selenium, Poloxamer 188, Polyethylene Glycol (PEG) 400, Sodium Chloride, and Phenyl mercuric nitrate was added and mixed to form the aqueous phase. The oil phase was added while stirring the aqueous phase with a high shear mixer to form the emulsion. This crude emulsion

was finely divided in a high pressure homogenizer to form a stable emulsion of antioxidants and the volume was made up with sufficient quantity of water for injection and the pH was adjusted using either sodium hydroxide/ hydrochloric acid and sterilized by filtration through 0.22 μm membrane filter to form the sterile ophthalmic emulsion of antioxidants, which is filled into containers aseptically and sealed.

In another embodiment of the invention, the ophthalmic emulsion comprises lutein, alpha tocopherol and pharmaceutical excipients.

Example: 3

Lutein + Alpha Tocopherol Ophthalmic Emulsion

S. No	Ingredient	mg/mL
1	Lutein	2 mg
2	Alpha Tocopherol	0.3mg
3	Medium Chain Triglycerides (MCT)	54 mg
5	Poloxamer 407	39 mg
6	Sodium Citrate	0.2 mg
7	Citric Acid	0.6mg
8	Benzalkonium Chloride	1 mg
9	Hydrochloric Acid/Sodium Hydroxide	q.s
10	Water for Injection	q.s

Process: Medium Chain Triglycerides was heated to about 70° C and to it was added Lutein, and alpha tocopherol and stirred to completely dissolve the same in the oil

phase. Sterile purified water was heated to about 70° C, and to it Poloxamer 407, Sodium Citrate, Citric Acid, and Benzalkonium Chloride was added and mixed to form the aqueous phase. The oil phase was added while stirring the aqueous phase with a high shear mixer to form the emulsion. This crude emulsion was finely divided in a high pressure homogenizer to form a stable emulsion of antioxidants and the volume was made up with sufficient quantity of water for injection and the pH was adjusted using either sodium hydroxide/ hydrochloric acid and sterilized by filtration through 0.22 µm membrane filter to form the sterile ophthalmic emulsion of antioxidants, which is filled into containers aseptically and sealed.

In another embodiment of the invention, the ophthalmic emulsion comprises of beta carotene and pharmaceutical excipients.

Example: 4

Beta Carotene Ophthalmic Emulsion

S. No	Ingredient	mg/mL
1	Beta Carotene	9 mg
2	Fish Oil	60 mg
3	Kolliphor EL (Polyethoxylated Castor Oil)	54 mg
4	Sodium Citrate	0.2 mg
5	Citric Acid	0.6mg
6	Benzalkonium Chloride	1 mg
7	Hydrochloric Acid/Sodium Hydroxide	q.s
8	Water for Injection	q.s

Process: Fish Oil was heated to about 70° C and it was added Beta carotene and stirred to completely dissolve the same in the oil phase. Sterile purified water was heated to about 70° C, and to it Kolliphor EL, Sodium Citrate, Citric Acid, and Benzalkonium Chloride were added and mixed to form the aqueous phase. The oil phase was added while stirring the aqueous phase with a high shear mixer to form the emulsion. This crude emulsion was finely divided in a high pressure homogenizer to form a stable emulsion of antioxidants and the volume was made up with sufficient quantity of water for injection and the pH was adjusted using either sodium hydroxide/ hydrochloric acid and sterilized by filtration through 0.22 µm membrane filter to form the sterile ophthalmic emulsion of antioxidants, which is filled into containers aseptically and sealed.

In another embodiment of the invention, the ophthalmic emulsion comprises of zeaxanthin and pharmaceutical excipients.

Example: 5 Zeaxanthin Ophthalmic Emulsion

S. No	Ingredient	mg/mL
1	Zeaxanthin	6 mg
2	Liquid Paraffin	69 mg
3	Polyethylene glycol oleyl ether (Brij® 93)	54 mg
4	Sodium borate	2 mg
5	Boric acid	6 mg
6	Benzalkonium Chloride	1 mg
7	Sorbitol	12 mg
8	Hydrochloric Acid/Sodium Hydroxide	q.s
9	Water for Injection	q.s

Process: Liquid Paraffin was heated to about 70° C and to it was added Zeaxanthin and stirred to completely dissolve the same in the oil phase. Sterile purified water was heated to about 70° C, and to it Polyethylene glycol oleyl ether (Brij® 93), Sodium Borate, Boric Acid, Sorbitol and Benzalkonium Chloride was added and mixed to form the aqueous phase. The oil phase was added to the aqueous phase while stirring the aqueous phase with a high shear mixer to form the emulsion. This crude emulsion was finely divided in a high pressure homogenizer to form a stable emulsion of antioxidants and the volume was made up with sufficient quantity of water for injection and the pH was adjusted using either sodium hydroxide/hydrochloric acid and sterilized by filtration through 0.22 µm membrane filter to form the sterile ophthalmic emulsion of antioxidants, which is filled into containers aseptically and sealed.

In another embodiment of the invention, the ophthalmic emulsion comprises of lutein and pharmaceutical excipients.

Example:6 Lutein Ophthalmic Emulsion

S. No	Ingredient	mg/mL
1	Lutein	3 mg
2	Jojoba oil	60 mg
3	Polyethylene glycol oleyl ether (Brij® 93)	45 mg
4	Sodium borate	2 mg
5	Boric acid	6 mg
6	Benzalkonium Chloride	1 mg
7	Sorbitol	12 mg
8	Hydrochloric Acid/Sodium Hydroxide	q.s

9	Water for Injection	q.s
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Process: Liquid Paraffin was heated to about 70° C and to it was added Lutein and stirred to completely dissolve the same in the oil phase. Sterile purified water was heated to about 70° C, and to it Polyethylene glycol oleyl ether (Brij® 93), Sodium Borate, Boric Acid, Sorbitol and Benzalkonium Chloride were added and mixed to form the aqueous phase. The oil phase was added to the aqueous phase while stirring the aqueous phase with a high shear mixer to form the emulsion. This crude emulsion was finely divided in a high pressure homogenizer to form a stable emulsion of antioxidants and the volume was made up with sufficient quantity of water for injection and the pH was adjusted using either sodium hydroxide/ hydrochloric acid and sterilized by filtration through 0.22 µm membrane filter to form the sterile ophthalmic emulsion of antioxidants, which is filled into containers aseptically and sealed.

The method for preparing the topical ocular suspension according to the disclosure described herein is not limited to the above methods. The ophthalmic emulsion for ocular delivery of antioxidants according to the disclosure described herein can be prepared by using various other techniques.

CLAIMS

We claim

1. A stable oil-in-water ophthalmic emulsion for ocular delivery of antioxidants comprising one or more antioxidants as an active pharmaceutical ingredient, at least one oil of vegetable, mineral or animal origin or a combination thereof, at least one surfactant and at least one pharmaceutically acceptable excipient, wherein the pH is in the range of about 4 to 8.
2. The stable oil-in-water ophthalmic emulsion of claim 1, wherein the antioxidant is selected from the group comprising of lutein, zeaxanthin, tocopherol, beta carotene, selenium or a combination thereof.
3. The stable oil-in-water ophthalmic emulsion of claim 1, wherein the concentration of antioxidant is in the range of about 0.0003%-0.3% w/v.
4. The stable oil-in-water ophthalmic emulsion of claim 1, wherein the oil is a vegetable oil or mineral oil or animal oil or a combination thereof.
5. The stable oil-in-water ophthalmic emulsion of claim 1, wherein the vegetable oil is selected from the group comprising of Castor Oil, Cotton seed Oil, Peanut Oil, Coconut oil, Rice bran oil, Sunflower oil, Sesame oil, Soyabean oil, Flax oil, Canola oil, Olive oil, Mustard Oil, Jojoba oil or a combination thereof.

6. The stable oil-in-water ophthalmic emulsion of claim 1, wherein the animal oil is selected from the group comprising of fish oil, shark liver oil, cod liver oil or a combination thereof.
7. The stable oil-in-water ophthalmic emulsion of claim 1, wherein the mineral oil is Liquid Paraffin and White Mineral Oil or a combination thereof.
8. The stable oil-in-water ophthalmic emulsion of claim 1, wherein the surfactant is selected from the group comprising of Polyoxyethylated nonionic surfactants like Polysorbate80, Polysorbate 60, Polysorbate, 40, Polysorbate 20, Cremophors, Tyloxapols, Poloxamers, Benzalkonium chloride, Benzethonium chloride, Cetyl alcohol, Carbomer, Cholesterol, Cocamidopropyl betaine, glyceryl monostearate, lanolin alcohols, lauralkonium chlorides, N lauroylsarcosine, Nonoxynol 9, Octoxynol 40, Polyoxyl 35 castor oil, Polyoxyl 40 hydrogenated castor oil. Polyoxyl 40 stearate, Sorbitanmonolaureate, Sorbitan monooleate, Sorbitanmonopalmitate, Polyoxyethylene (2) Steryl Ether, Polyoxyethylene (2) Cetyl Ether, Polyoxyethylene (2) Oleyl Ether, Polyoxyethylene (2) Nonylphenylether, Polyoxyethylene (2) isooctylphenyl ether, Polyoxyethylene (4) lauryl ether, Polyoxyethylene (5) isooctylphenylether or a combination thereof.
9. The stable oil-in-water ophthalmic emulsion of claim 1, further comprises at least one pH adjusting agent selected from the group comprising of Hydrochloric Acid, Sodium Hydroxide, Sulphuric Acid, Sodium Sulphate, Acetic Acid, Sodium Citrate, Ammonium Hydroxide, Citric Acid, Diethanolamine, Nitric Acid, Phosphoric Acid or a combination thereof.

10. The stable oil-in-water ophthalmic emulsion of claim 1, further comprises at least one buffering agent selected from the group comprising of Acetic Acid, Boric Acid, Citric Acid, Phosphoric Acid, Potassium Acetate, Potassium Phosphate, Potassium Sulphate, Potassium Sorbate, Sodium Acetate, Sodium borate, Sodium Carbonate, Sodium Citrate, Sodium Phosphate, Sorbic Acid, Tromethamine or a combination thereof.
11. The stable oil-in-water ophthalmic emulsion of claim 1, further comprises at least one osmolarity control agent selected from the group comprising of Sodium Chloride, Sodium Sulphate, Sodium Nitrate, Sorbitol, Mannitol, Calcium Chloride, Glycerine, Magnesium Chloride, PEG 300, PEG 400, Potassium Chloride, Propylene Glycol or a combination thereof.
12. The stable oil-in-water ophthalmic emulsion of claim 1, further comprises at least one antimicrobial preservative selected from the group comprising of Quaternary ammonium compounds selected from Benzalkonium Chloride, Benzethonium chloride, Benzododecinium bromide or Polyquaternium-1; or Acid/Base compounds selected from Boric acid, sodium acetate or sodium borate; or Alcohols selected from chlorobutanol or Phenylethyl alcohol; or Organic Mercuric compounds selected from Phenyl mercuric acetate, Phenyl mercuric nitrate or Thimerosal; or Parabens selected from methyl paraben or Propyl Paraben; or Oxidizing agent sodium chlorite; or Metal salt Zinc Chloride or a combination thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2018/050170

A. CLASSIFICATION OF SUBJECT MATTER
A61K36/00, A61K9/10, A61K31/355, A61K47/10 Version=2018.01

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)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US20130108674 A1 (MEDIVIS S.R.L., 02 MAY, 2013) whole document, abstract, example 5, claim 1, 5-10	1-12
X	US5496811 A (PHARMOS CORP, 5 MARCH, 1996) example 1, claims 1,3-5, 7-10, 19	1-12
A	US20130253070 A1 (GUPRON GMBH, 26 SEPTEMBER, 2013) abstract, para 52-55, 57, 59, 60	1-12
A	US20140170247 A1 (GUARDION HEALTH SCIENCES LLC, 19 JUNE, 2014) para 42, 43, 47, 48, 54, 57-60; claims 1, 4, 5, 9, 10	1-12

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

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
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"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 29-06-2018	Date of mailing of the international search report 29-06-2018
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Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14, Dwarka, New Delhi-110075 Facsimile No.	Authorized officer Ravi S Telephone No. +91-1125300200
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2018/050170

Citation	Pub.Date	Family	Pub.Date
US 20130108674 A1	02-05-2013	WO 2011154985 A1	15-12-2011
		EP 2579845 A1	17-04-2013
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