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(71) Applicant: **SUN PHARMACEUTICAL INDUSTRIES LIMITED** [IN/IN]; Sun House, Plot No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai, Maharashtra 400 063 (IN).

(72) Inventors: **RAO, Rajesh**; Village Mundera, Mahuawabazrat, Deoria, Uttar Pradesh 274408 (IN). **FANDA, Anuj Kumar**; SPS Residency, Flat No. GH-101, 18-B, Vaibhav Khand, Indrapuram, Ghaziabad, Uttar Pradesh 201014 (IN). **JAIN, Satish Kumar**; D-18, Mincoha Colony, Bilaspur, Chhattisgarh 495001 (IN). **SINGH, Romi Barat**; A-14, Badshah Bagh, Varanasi, Uttar Pradesh 221002 (IN).

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(54) Title: STABLE NANOEMULSION COMPOSITION

(57) Abstract: The present invention relates to a thermodynamically and kinetically stable clear nanoemulsion composition comprising a surfactant in an amount of less than about 10% w/w of the total composition, and a process for its preparation. Surfactants in high concentration irritate the mucosa. The tolerability of compositions with high amounts of surfactants may be poor in cases where chronic administration is intended. Chronic oral administration of compositions with high concentrations of surfactant may lead to adverse effects such as diarrhea.



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STABLE NANOEMULSION COMPOSITION

Field of the Invention

The present invention relates to a thermodynamically and kinetically stable clear nanoemulsion composition comprising a surfactant in an amount of less than about 10% w/w of the total composition, and a process for its preparation.

Background of the Invention

Nanoemulsions are emulsion systems of oil, water, surfactants, and optionally co-solvents, with a droplet size in the range of about 5 nm to about 500 nm. Usually, the average droplet size is between 20 nm and 200 nm. Nanoemulsions are also referred to as mini-emulsions, ultrafine emulsions, and sub-micron emulsions. Nanoemulsions have found wide applications in drug delivery of poorly soluble active agents. They enhance solubility, resulting in improved bioavailability of the active agents.

Nanoemulsions with a small droplet size have an added benefit of being translucent or even transparent. But droplet size may increase over time due to coalescence, flocculation, and/or Ostwald ripening. The small size of droplets of nanoemulsions makes them particularly prone to Ostwald ripening. An increase in droplet size over time is disadvantageous as the emulsion will lose its clarity. To overcome this problem, the nanoemulsions contain relatively higher amounts of surfactants to stabilize the nano-droplets.

Ammar *et al.*, AAPS PharmSciTech, 10(3):808-819 (2009) discloses nanoemulsion compositions of dorzolamide for ophthalmic use. These nanoemulsions contain more than 12% w/w of the surfactant. Ophthalmic dosage forms contain relatively lesser amounts of active agent and thus, the amount of active agent that needs to be loaded in a nanoemulsion for ophthalmic use is relatively lower. Further, these nanoemulsions, when subjected to freeze-thaw cycle test and stored at -21°C, turned turbid and the coagulation of internal phase at low temperature may be responsible for the instability.

Malgope *et al.*, International Journal of Pharmaceutical and Chemical Sciences, 2(4):1655-1665 (2013) discloses nanoemulsions of valsartan to be used in transdermal delivery. This document discloses various nanoemulsion compositions comprising triacetin (a short chain glyceride) as an oily component and surfactant in amounts of less than 10% w/w and also above 10% w/w of the total composition. However, compositions

comprising a surfactant in an amount of less than 10% w/w of total composition failed the freeze-thaw test and were not selected further for the experiments and development.

PCT Publication No. WO 2009/067734 discloses a nanoemulsion comprising long chain triglycerides having a chain length of 12 carbon atoms or greater. This patent
5 publication discloses that when medium chain triglycerides were used as the oil phase, high clarity nanoemulsions were obtained. However, these nanoemulsions were prone to Ostwald ripening and droplet size increased such that the nanoemulsion lost its clarity.

The present invention provides a clear nanoemulsion composition comprising a medium-chain or a short-chain glyceride or mixtures thereof as an oily phase; and a
10 surfactant in an amount of less than about 10% w/w of the total composition, wherein said composition is thermodynamically and kinetically stable.

Summary of the Invention

Surfactants in high concentration irritate the mucosa. The tolerability of compositions with high amounts of surfactants may be poor in cases where chronic
15 administration is intended. Chronic oral administration of compositions with high concentrations of surfactant may lead to adverse effects such as diarrhea. Topical administration of such compositions can cause irritation to the skin and mucosal membranes. On parenteral administration, high concentrations of surfactant may cause lysis of human red blood cells. Furthermore, the WHO and the US FDA have placed
20 restrictions on the daily intake of many of the commonly used surfactants. On the other hand, developing a stable nanoemulsion with a low concentration of surfactants presents significant challenges to the formulation scientists. The present invention provides a thermodynamically and kinetically stable clear nanoemulsion composition comprising medium-chain or a short-chain glyceride or mixtures thereof as an oily phase, and a low
25 amount of surfactant, particularly less than about 10% w/w of the total composition. The advantages of using medium-chain or a short-chain glyceride over a long chain glyceride is that they are easy to emulsify and yield high clarity nanoemulsions.

Detailed Description of the Invention

A first aspect of the present invention provides a clear nanoemulsion composition
30 comprising:

- a) an active ingredient;

- b) an oily phase selected from the group consisting of a medium-chain or a short-chain glyceride or mixtures thereof;
- c) a surfactant;
- d) optionally, a co-solvent; and
- 5 e) an aqueous phase

wherein the surfactant is present in an amount of less than about 10% w/w of the total composition, and said composition is thermodynamically and kinetically stable.

The oily phase of the nanoemulsion composition of the present invention comprises either a medium-chain glyceride, a short-chain glyceride, or mixtures thereof.

- 10 The oily phase is present in an amount of about 5% w/w to about 25% w/w of the total composition.

The term “medium-chain glyceride” as used herein refers to mono-, di-, or tri-glycerides or polyoxylglycerides of fatty acids with a chain length of 8 to 12 carbon atoms. The medium-chain glyceride is, for example, and without limitation fractionated coconut oil or palm seed oil; glycerides of caprylic/capric acid, *e.g.*, Miglyol[®], Captex[®], tricaprylin, Labrafac[™] Lipophile, Imwitor[®], akoline, Labrasol[®], and Sefsol[™]; glycerides of lauric acid, *e.g.*, Gelucire[®] 44/14; or mixtures thereof.

- The term “short-chain glyceride” as used herein refers to mono-, di-, or tri-glycerides or polyoxylglycerides of fatty acids with a chain length of 1 to 7 carbons atoms.
- 20 The short-chain glyceride is, for example, and without limitation, triacetin, tripropionin, tributyrin, trihexanoin, triheptanoin, or mixtures thereof. In particular, the short-chain glyceride is triacetin.

“Surfactants” are the agents that decrease the interfacial tension between two liquids, or between a liquid and a solid, thus allowing an easier spreading. Surfactants may be anionic, cationic, or non-ionic, more particularly surfactants of HLB value of more than 10. The surfactant is, for example, and without limitation, polysorbates, *e.g.*, polysorbate 20, polysorbate 40, polysorbate 60, and polysorbate 80; polyethylene glycol alkyl ethers; sugar esters, *e.g.*, sucrose palmitate, sucrose laurate, sucrose distearate and monostearate (Crodesta[™] F110), sucrose monostearate (Crodesta[™] F160), and saccharose monolaurate; polyethoxylated fatty acids; polyoxyethylene-polyoxypropylene block co-polymers also known as ‘poloxamers’ available under various trade names, *e.g.*,

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Synperonic[®] PE series, Pluronic[®] series, Lutrol[®], Pluracare[®], and Plurodac; polyethylene glycol alkyl phenol ethers; citric acid esters of monoglycerides; polyglycerol esters; polyethoxylated fatty acid diesters; PEG-fatty acid mono and diesters; polyethylene glycol glycerol fatty acid esters; alcohol oil trans-esters; sodium lauryl sulphate; sodium oleate, potassium oleate; or mixtures thereof. In particular, the surfactant is a non-ionic surfactant, more particularly the non-ionic surfactant is polysorbate 80. Non-ionic surfactants are relatively less toxic than their ionic counterparts and have lower critical micelle concentrations. The non-ionic surfactant is present in an amount of less than about 10% w/w of the total composition, in particular from about 5% w/w to less than about 10% w/w of the total composition.

The term “co-solvent” as used herein refers to the agents that act synergistically with surfactants to facilitate in the dispersion process. The co-solvent is, for example, and without limitation, C₁-C₁₀ alcohols, *e.g.*, methanol, ethanol, propanol, iso-propyl alcohol, butanol, pentanol, hexanol, heptanol, octanol, nonanol, and decanol; polyols, *e.g.*, glycerol, propylene glycol, polyethylene glycol, and polypropylene glycol; diethylene glycol monoethyl ethers (Transcutol[®]); or mixtures thereof. In particular, the co-solvent is propylene glycol. The co-solvent is present in an amount of about 20% w/w to about 60% w/w of the total composition. The ratio of surfactant to co-solvent in nanoemulsion composition of the present invention is between 1:2 and 1:6, in particular the ratio is 1:3 to 1:5.

The aqueous phase of the nanoemulsion composition of the present invention comprises purified or ultrapure water, saline, or buffered saline. The amount of aqueous phase in the nanoemulsion may be from about 30% w/w to about 70% w/w of the total composition.

The term “clear nanoemulsion” as used herein refers to the nanoemulsions that are transparent and are visually clear with no signs of turbidity. Further, upon infinite dilution with an aqueous phase, they form true solutions. The average globule size of the nanoemulsion composition of the present invention is from about 5 nm to about 200 nm, in particular the average globule size is from about 5 nm to about 100 nm.

“Average globule size” refers to Z-average globule size. The Z-average globule size is the mean diameter based on the intensity of light scattered, as determined using a Nanosizer or Zetasizer, based on the principle of dynamic light scattering.

“Thermodynamically stable” refers to nanoemulsions showing no signs of phase separation, creaming, or cracking when subjected to extreme temperature. At low temperature values of less than 10°C, in particular between 0°C and -21°C the oily phase is rejected leading to phase separation and instability. High temperature values of equal to
5 or more than 40°C result in isotropic clear solutions. “Kinetically stable” refers to nanoemulsions showing no signs of coalescence, flocculation, and/or Ostwald ripening over a period of time.

According to one embodiment of this aspect, the medium-chain glyceride is, for example, and without limitation, fractionated coconut oil or palm seed oil, glycerides of
10 caprylic/capric acid, glycerides of lauric acid, or mixtures thereof.

According to another embodiment of this aspect, the short-chain glyceride is, for example, and without limitation, triacetin, tripropionin, tributyrin, trihexanoin, triheptanoin, or mixtures thereof.

According to another embodiment of this aspect, the short-chain glyceride is
15 triacetin.

According to another embodiment of this aspect, the surfactant is a non-ionic surfactant.

According to yet another embodiment of this aspect, the non-ionic surfactant is, for example, and without limitation, polysorbates, polyethylene glycol alkyl ethers, sugar
20 esters, polyethoxylated fatty acids, polyoxyethylene-polyoxypropylene block co-polymers, polyethylene glycol alkyl phenol ethers, citric acid esters of monoglycerides, polyglycerol esters, polyethoxylated fatty acid diesters, sorbitan fatty acid esters, PEG-fatty acid mono and diesters, polyethylene glycol glycerol fatty acid esters, alcohol oil trans-esters, or mixtures thereof.

According to yet another embodiment of this aspect, the non-ionic surfactant is
25 polysorbate, for example, and without limitation, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, or mixtures thereof.

According to yet another embodiment of this aspect, the non-ionic surfactant is polysorbate 80.

According to yet another embodiment of this aspect, the co-solvent is, for example, and without limitation, C₁-C₁₀ alcohol, polyols, diethylene glycol monoethyl ether, or

mixtures thereof.

According to yet another embodiment of this aspect, the co-solvent is a polyol.

According to yet another embodiment of this aspect, the polyol is propylene glycol.

5 According to yet another embodiment of this aspect, the average globule size is from about 5 nm to about 200 nm.

According to yet another embodiment of this aspect, the average globule size is from about 5 nm to about 100 nm.

10 According to yet another embodiment of this aspect, the composition is prepared by a simple mixing process comprising:

- i) mixing a medium-chain or a short-chain glyceride or mixtures thereof, a non-ionic surfactant, a co-solvent, and an aqueous phase to obtain a nanoemulsion; and
- 15 ii) adding an active ingredient to the nanoemulsion of step i) followed by mixing to obtain an active ingredient-loaded nanoemulsion.

A second aspect of the present invention provides a clear nanoemulsion composition comprising:

- a) active ingredient;
- b) triacetin;
- 20 c) polysorbate 80 in an amount of about 5% to less than about 10%;
- d) propylene glycol; and
- e) water

wherein said composition is thermodynamically and kinetically stable.

25 According to one embodiment of this aspect, triacetin is present in an amount of about 5% w/w to about 25% w/w of the total composition.

According to still one more embodiment of this aspect, propylene glycol is present in an amount of about 20% w/w to about 60% w/w of the total composition.

According to another embodiment of this aspect, water is present in an amount of about 30% w/w to about 70% w/w of the total composition.

According to yet another embodiment of this aspect, the composition is prepared by a simple mixing process comprising:

- i) mixing triacetin, polysorbate 80, propylene glycol, and water to obtain a nanoemulsion; and
- 5 ii) adding an active ingredient to the nanoemulsion of step i) followed by mixing to obtain an active ingredient-loaded nanoemulsion.

To assess the thermodynamic stability, the compositions of the invention were subjected to heating-cooling cycles, freeze-thaw cycles, and dispersibility tests:

1. Heating-cooling cycle: The compositions were exposed to six cycles between refrigerator temperature (4°C) and 40°C, with storage at each temperature for not less than 48 hours, followed by visual examination of the compositions for signs of phase separation.
2. Freeze-thaw cycle: The compositions were exposed to three freeze-thaw cycles between -21°C and 25°C, with storage at each temperature for not less than 48 hours, followed by visual examination of the compositions for signs of phase separation.
3. Dispersibility test: One mL of each composition was added to 500 mL of water in a dissolution assembly maintained at 37°C ±0.5°C, followed by visual examination of the compositions for signs of phase separation and transparency. On infinite dilution of nanoemulsion composition, there is a high possibility of phase separation leading to precipitation of the active ingredient. This process is thermodynamically driven by the requirement of the surfactant to maintain an aqueous phase concentration equivalent to its critical micelle concentration (CMC).

To assess the kinetic stability, the compositions of the present invention were kept in closed vials at room temperature for at least one month, followed by visual examination of the compositions for turbidity or loss of clarity.

Any suitable active ingredient can be incorporated into the nanoemulsion composition of the present invention. Examples of active ingredients include, but are not limited to, hormones, *e.g.*, insulin, calcitonin, somatropin, somatotropin, somatostatin, insulin-like growth factor, luteinizing hormone releasing hormone, growth hormones, growth hormone releasing hormone, sex hormones, parathyroid hormone, and calcitonin; hematological agents; anticoagulants; hematopoietic agents; hemostatics; thrombolytic

agents; endocrine agents; anti-diabetic agents; anti-thyroid agents; beta-adrenoceptor blocking agents; biphosphonates; uterine-active agents; cardiovascular agents; anti-arrhythmic agents; anti-anginal agents; anti-hypertensive agents; vasodilators; agents used in treatment of heart disorders; cardiac inotropic agents; renal agents; genitourinary
5 agents; antidiuretic agents; respiratory agents; antihistamines; cough suppressants; parasympathomimetics; sympathomimetics; xanthines; central nervous system agents; analgesics; anesthetics; anti-emetic agents; anorexiant; anti-depressants; anti-migraine agents; anti-epileptics; dopaminergics; anti-cholinergics; anti-parkinsonian agents; muscle relaxants; narcotic antagonists; sedatives; stimulants; treatments for attention deficit
10 disorder; immunosuppressive agents; gastrointestinal agents; systemic anti-infectives; agents used in the treatment of AIDS; anti-helminthics; anti-mycobacterial agents; vaccines; hormones; dermatological agents; elastase inhibitors; anti-muscarinic agents; lipid regulating agents; and antineoplastic agents. In particular, the active ingredient is acitretin, isotretinoin, amiodarone, cefpodoxime proxetil, atorvastatin, azithromycin,
15 carvedilol, cyclosporine, or digoxin. The amount of active ingredient that can be loaded into the nanoemulsion of present invention is from about 0.05% w/w to about 20% w/w of the total composition, in particular from about 0.1% w/w to about 5% w/w of the total composition.

The nanoemulsions of the present invention are suitable for administration via any
20 of the well-known routes including oral, parenteral, ophthalmic, otic, and topical/transdermal routes.

The nanoemulsion of the present invention may further contain additives, *e.g.*, stabilizers, antioxidants, preservatives, buffering agents, charge inducing agents, polymers, and proteins. Stabilizers can be anti-creaming or anti-foaming agents or any
25 other agents which impart stability to the nanoemulsion.

The term "about" as used herein refers to any value which lies within the range defined by a variation of up to $\pm 10\%$ of the value.

The following examples illustrate the invention but are not to be construed as limiting the scope of the invention.

EXAMPLES

Examples 1-7

Ingredients	Percentage (% w/w)						
	1	2	3	4	5	6	7
Triacetin	4.00	4.00	6.00	5.00	20.00	5.00	10.00
Water	60.00	66.00	54.00	55.00	25.00	35.00	30.00
Polysorbate 80	6.00	6.00	8.00	10.00	10.00	10.00	10.00
Propylene glycol	30.00	24.00	32.00	30.00	45.00	50.00	50.00
Total composition	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Process:

- 5 Triacetin, polysorbate 80, and propylene glycol were mixed with water using a blender to obtain a clear nanoemulsion.

Stability Studies:

- 10 All of the nanoemulsion compositions prepared according to Examples 1-7 were subjected to heating-cooling cycles, freeze-thaw cycles, and dispersibility tests. All of the nanoemulsion compositions were found to be thermodynamically stable with no phase separation, creaming, or cracking.

- 15 Further, all of the nanoemulsion compositions prepared according to Examples 1-7 were kept in closed vials at room temperature for a period of one month and were visually examined for turbidity or loss of clarity. All of the nanoemulsion compositions were found to be kinetically stable showing no signs of coalescence, flocculation, or Ostwald ripening.

Globule Size

The globule size of nanoemulsion of Example 6 was measured using Zetasizer. The average globule size (Z-average globule size) was found out to be 11.93 nm.

- 20 **Loading of active ingredient into nanoemulsion composition:**

A suitable active agent was added to the nanoemulsion of Example 6 and mixed to obtain an active ingredient-loaded nanoemulsion. Ten mg of cefpodoxime proxetil was dissolved in one g of the nanoemulsion to yield a clear active-ingredient loaded nanoemulsion.

We claim:

- 1 1. A clear nanoemulsion composition comprising:
 - 2 a) an active ingredient;
 - 3 b) an oily phase selected from the group consisting of a medium-chain or a short-
 - 4 chain glyceride or mixtures thereof;
 - 5 c) a surfactant;
 - 6 d) optionally, a co-solvent; and
 - 7 e) an aqueous phase
- 8 wherein the surfactant is present in an amount of less than about 10% w/w of the total
- 9 composition and said composition is thermodynamically and kinetically stable.
- 1 2. The composition according to claim 1, wherein the medium-chain glyceride is
- 2 selected from the group consisting of fractionated coconut oil or palm seed oil, glycerides
- 3 of caprylic/capric acid, glycerides of lauric acid, and mixtures thereof.
- 1 3. The composition according to claim 1, wherein the short-chain glyceride is
- 2 selected from the group consisting of triacetin, tripropionin, tributyrin, trihexanoin,
- 3 triheptanoin, and mixtures thereof.
- 1 4. The composition according to claim 3, wherein the short-chain glyceride is
- 2 triacetin.
- 1 5. The composition according to claim 1, wherein the surfactant is a non-ionic
- 2 surfactant.
- 1 6. The composition according to claim 5, wherein the non-ionic surfactant is selected
- 2 from the group consisting of polysorbates, polyethylene glycol alkyl ethers, sugar esters,
- 3 polyethoxylated fatty acids, polyoxyethylene-polyoxypropylene block co-polymers,
- 4 polyethylene glycol alkyl phenol ethers, citric acid esters of monoglycerides, polyglycerol
- 5 esters, polyethoxylated fatty acid diesters, sorbiton fatty acid esters, PEG-fatty acid mono
- 6 and diesters, polyethylene glycol glycerol fatty acid esters, alcohol oil trans-esters, and
- 7 mixtures thereof.
- 1 7. The composition according to claim 6, wherein the non-ionic surfactant is
- 2 polysorbate selected from the group comprising polysorbate 20, polysorbate 40,
- 3 polysorbate 60, polysorbate 80, and mixtures thereof.

- 1 8. The composition according to claim 7, wherein the polysorbate is polysorbate 80.
- 1 9. The composition according to claim 1, wherein the co-solvent is selected from the
2 group consisting of C₁-C₁₀ alcohol, polyols, diethylene glycol monoethyl ether, and
3 mixtures thereof.
- 1 10. The composition according to claim 9, wherein the co-solvent is a polyol.
- 1 11. The composition according to claim 10, wherein the polyol is propylene glycol.
- 1 12. The composition according to claim 1, wherein the average globule size is from
2 about 5 nm to about 200 nm.
- 1 13. The composition according to claim 12, where the average globule size is from
2 about 5 nm to about 100 nm.
- 1 14. The composition according to claim 1, is prepared by a simple mixing process
2 comprising:
- 3 i) mixing a medium-chain or a short-chain glyceride or mixtures thereof as oily
4 phase, a surfactant, and optionally a co-solvent in an aqueous phase to obtain a
5 nanoemulsion; and
- 6 ii) adding an active ingredient to the nanoemulsion of step i) to obtain an active
7 ingredient-loaded nanoemulsion.
- 1 15. A clear nanoemulsion composition comprising:
- 2 i) active ingredient
3 ii) triacetin;
4 iii) about 5% w/w to about 10% w/w of polysorbate 80;
5 iv) propylene glycol; and
6 v) water
- 7 wherein said composition is thermodynamically and kinetically stable.
- 1 16. The composition according to claim 15, wherein triacetin is present in an amount
2 of about 5% w/w to about 25% w/w of the total composition.
- 1 17. The composition according to claim 15, wherein propylene glycol is present in an
2 amount of about 20% w/w to about 60% w/w of the total composition.

1 18. The composition according to claim 15, wherein water is present in an amount of
2 about 30% w/w to about 70% w/w of the total composition.

1 19. The composition according to claim 15, is prepared by a simple mixing process
2 comprising:

3 i) mixing triacetin, polysorbate 80, propylene glycol, and water to obtain a
4 nanoemulsion; and,

5 ii) adding an active ingredient to the nanoemulsion of step i) to obtain an active
6 ingredient-loaded nanoemulsion.

1 20. The composition according to any of preceding claims 1-19, wherein said
2 composition is suitable for administration through oral, parenteral, ophthalmic, otic,
3 topical or transdermal route.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2015/054092

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 8/06 (2015.01)

CPC - A61K 8/068 (2015.09)

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(8) - A61K 8/06, 9/107, 47/10; A61Q 19/00 (2015.01)

CPC - A61K 8/068, 9/107, 47/10; A61Q 19/00 (2015.09)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC -424/400; 514/786; CPC - A61K 8/068, 9/107, 47/10; A61Q 19/00 (2015.09) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Orbit, Google Scholar.

Search terms used: clear, nanoemulsion, mediumchain, shortchain, glyceride, surfactant, thermodynamically, kinetically, stable, triacetin, tripropionin, tributyrin, trihexanoin, triheptanoin, polysorbate, polysorbate 80

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0305218 A1 (WOOSTER et al) 02 December 2010 (02.12.2010) entire document	1-20
A	US 5,698,219 A (VALDIVIA et al) 16 December 1997 (16.12.1997) entire document	1-20
A	US 2003/0087967 A1 (QUEMIN) 08 May 2003 (08.05.2003) entire document	1-20
A	US 8,722,131 B2 (TANG et al) 13 May 2014 (13.05.2014) entire document	1-20
A	US 2009/0208541 A1 (GESZTESI et al) 20 August 2009 (20.08.2009) entire document	1-20
A	US 8,357,639 B2 (QUINTERO et al) 22 January 2013 (22.01.2013) entire document	1-20



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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