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(54) **Title**: COMPOSITION AND METHOD

(57) **Abstract**: A method of preparing a composition comprises an active agent which is at least partially enclosed in a polymersome in a liquid formulation. The method comprises admixing the active agent, the agents required for forming the polymersome and a liquid formulation, and allowing / causing polyrmersome formation.

COMPOSITION AND METHOD

The present invention relates to a method of delivering an active agent to a locus and to a method of preparing a composition for use in same.

In certain compositions, such as cleaning compositions, consumers are aware that in order to achieve effective cleaning of household items and surfaces often multiple separate actives have to be employed. Bleaches are able to act upon stains and can cause the chemical disruption (oxidation) of the stain and / or its decolouration, and thus masking of the stain. Bleaches also provide an anti-microbial action. Enzymes are required for stain treatment. Surfactants for grease treatment and builders to control the level of metals in wash liquor. Each of these ingredients may also require a supplement or additive to work effectively.

One major issue with the use of multiple active components is that due to their reactivity (and inter-reactivity) typically they must be kept separate until the desired point of use. This is relatively facile when the overall composition is in solid form since any inter-reaction is prevented. Thus cleaning powders and compressed particulate tablets can be produced which contain both bleach and bleach activator in solid form. Additionally often reactive components are segregated with the composition as a further aid to prevent premature reaction.

However, certain cleaning preparations require the use of a liquid bleaching formulation. In such a case the facile separation solution cannot easily be achieved since the detersive components are free to migrate within the liquid and will, if they

come into contact, react with one another. Thus traditionally it has been necessary to provide liquid cleaning formulations in multi-chamber packs, wherein one chamber contains some actives (e.g. bleach) and one chamber contains other actives (e.g. a bleach activator), so that the agents only brought into contact at the point of use. Such twin chamber packs are expensive to manufacture and cumbersome in use, requiring an unnecessary burden of dexterity from a consumer.

It is an object of the present invention to obviate / mitigate the disadvantages described above.

According to a first aspect of the invention there is provided A method of preparing a composition comprising an active agent which is at least partially enclosed in a polymersome in a liquid formulation comprising admixing the active agent, the agents required for forming the polymersome and a liquid formulation, and allowing / causing polymersome formation.

It has been found that the composition provides control/sustained release of the active agents, for example at the site of use. This, in turn gives an enhanced local effect - more performance, longer lasting effect through controlled release or the same performance from less of the active agent.

The composition also provide excellent segregation of the active agent from the reminder of the composition and the surrounding environment.

Preferably the active agent comprises phenylyepherine, pseudoepherine, ibuprofen (and its salt forms), flurbiprofen (and its salt forms), ketoprofen (and its salt forms), diclofenac (and its salt forms), and / or paracetemol. Alternatively the active agent comprises an enzyme, a bleach, a bleach activator, and / or a polymer.

Preferably the disruption mechanism is a chemical and / or mechanical disruption. Preferred disruption mechanisms include the application of mechanical shear and / or change in osmotic potential.

Preferably the method is for use in treating a condition.

"Polymersomes" are vesicles, which are assembled from synthetic multi-block polymers in aqueous solutions. Unlike liposomes, a polymersome does not include lipids or phospholipids as its majority component. Consequently, polymersomes can be thermally, mechanically, and chemically distinct and, in particular, more durable and resilient than the most stable of lipid vesicles. The polymersomes assemble during processes of lamellar swelling, e.g., by film or bulk rehydration or through an additional phoresis step, as described below, or by other known methods. Like liposomes, polymersomes form by "self assembly," a spontaneous, entropy-driven process of preparing a closed semi-permeable membrane.

Because of the perselectivity of the bilayer, materials may be "encapsulated" in the aqueous interior (lumen) or intercalated into the hydrophobic membrane core of the polymersome vesicle, forming a "loaded polymersome". Numerous technologies can be developed from such vesicles, owing to the numerous unique features of the bilayer membrane and the broad availability of super-amphiphiles, such as diblock, triblock, or other multi-block copolymers.

The synthetic polymersome membrane can exchange material with the "bulk," i.e., the solution surrounding the vesicles. Each component in the bulk has a partition coefficient, meaning it has a certain probability of staying in the bulk, as well as a probability of remaining in the membrane. Conditions can be predetermined so that the partition coefficient of a selected

type of molecule will be much higher within a vesicle's membrane, thereby permitting the polymersome to decrease the concentration of a molecule, such as cholesterol, in the bulk. In a preferred embodiment, phospholipid molecules have been shown to incorporate within polymersome membranes by the simple addition of the phospholipid molecules to the bulk. In the alternative, polymersomes can be formed with a selected molecule, such as a hormone, incorporated within the membrane, so that by controlling the partition coefficient, the molecule will be released into the bulk when the polymersome arrives at a destination having a higher partition coefficient.

Polymersomes may be formed from synthetic, amphiphilic copolymers. An "amphiphilic" substance is one containing both polar (water-soluble) and hydrophobic (water-insoluble) groups. "Polymers" are macromolecules comprising connected monomeric units. The monomeric units may be of a single type (homogeneous), or a variety of types (heterogeneous). The physical behavior of the polymer is dictated by several features, including the total molecular weight, the composition of the polymer (e.g., the relative concentrations of different monomers), the chemical identity of each monomeric unit and its interaction with a solvent, and the architecture of the polymer (whether it is single chain or branched chains). For example, in polyethylene glycol (PEG), which is a polymer of ethylene oxide (EO), the chain lengths which, when covalently attached to a phospholipid, optimize the circulation life of a liposome, is known to be in the approximate range of 34-114 covalently linked monomers (EO34 to EO114).

The preferred class of polymer selected to prepare the polymersomes is the "block copolymer." Block copolymers are polymers having at least two, tandem, interconnected regions of differing chemistry. Each region comprises a repeating sequence of mono-

mers. Thus, a "diblock copolymer" comprises two such connected regions (A-B); a "triblock copolymer," three (A-B-C), etc. Each region may have its own chemical identity and preferences for solvent. Thus, an enormous spectrum of block chemistries is theoretically possible, limited only by the acumen of the synthetic chemist.

In the "melt" (pure polymer), a diblock copolymer may form complex structures as dictated by the interaction between the chemical identities in each segment and the molecular weight. The interaction between chemical groups in each block is given by the mixing parameter or Flory interaction parameter, [chi], which provides a measure of the energetic cost of placing a monomer of A next to a monomer of B. Generally, the segregation of polymers into different ordered structures in the melt is controlled by the magnitude of [chi]N, where N is proportional to molecular weight. For example, the tendency to form lamellar phases with block copolymers in the melt increases as [chi]N increases above a threshold value of approximately 10.

A linear diblock copolymer of the form A-B can form a variety of different structures. In either pure solution (the melt) or diluted into a solvent, the relative preferences of the A and B blocks for each other, as well as the solvent (if present) will dictate the ordering of the polymer material. In the melt, numerous structural phases have been seen for simple AB diblock copolymers.

To form a stable membrane in water, the absolute minimum requisite molecular weight for an amphiphile must exceed that of methanol $HOCH_3$, which is undoubtedly the smallest canonical amphiphile, with one end polar (HO-) and the other end hydrophobic ($-CH_3$). Formation of a stable lamellar phase more precisely requires an amphiphile with a hydrophilic group whose projected

area, when viewed along the membrane's normal, is approximately equal to the volume divided by the maximum dimension of the hydrophobic portion of the amphiphile (Israelachvili, in Intermolecular and Surface Forces, 2 less than nd ed., Pt3 (Academic Press, New York) 1995).

The most common lamellae-forming amphiphiles also have a hydrophilic volume fraction between 20 and 50 percent. Such molecules form, in aqueous solutions, bilayer membranes with hydrophobic cores never more than a few nanometers in thickness. The present invention relates to polymserosmes with all super-amphiphilic molecules which have hydrophilic block fractions within the range of 20-50 percent by volume and which can achieve a capsular state. The ability of amphiphilic and super-amphiphilic molecules to self-assemble can be largely assessed, without undue experimentation, by suspending the synthetic super-amphiphile in aqueous solution and looking for lamellar and vesicular structures as judged by simple observation under any basic optical microscope or through the scattering of light.

For typical phospholipids with two acyl chains, temperature can affect the stability of the thin lamellar structures, in part, by determining the volume of the hydrophobic portion. In addition, the strength of the hydrophobic interaction, which drives self-assembly and is required to maintain membrane stability, is generally recognized as rapidly decreasing for temperatures above approximately 50°C. Such vesicles generally are not able to retain their contents for any significant length of time under conditions of boiling water.

Upper limits on the molecular weight of synthetic amphiphiles which form single component, encapsulating membranes clearly exceed the many kilodalton range, as concluded from the work of Discher et al., (1999).

Block copolymers with molecular weights ranging from about 2 to 10 kilograms per mole can be synthesized and made into vesicles when the hydrophobic volume fraction is between about 20 percent and 50 percent. Diblocks containing polybutadiene are prepared, for example, from the polymerization of butadiene in cyclohexane at 40°C using sec-butyllithium as the initiator. Microstructure can be adjusted through the use of various polar modifiers. For example, pure cyclohexane yields 93 percent 1.4 and 7 percent 1.2 addition, while the addition of THF (50 parts per Li) leads to 90 percent 1.2 repeat units. The reaction may be terminated with, for example, ethyleneoxide, which does not propagate with a lithium counterion and HCl, leading to a monofunctional alcohol. This PB-OH intermediate, when hydrogenated over a palladium (Pd) support catalyst, produces PEE-OH. Reduction of this species with potassium naphthalide, followed by the subsequent addition of a measured quantity of ethylene oxide, results in the PEO-PEE diblock copolymer. Many variations on this method, as well as alternative methods of synthesis of diblock copolymers are known in the art; however, this particular preferred method is provided by example, and one of ordinary skill in the art would be able to prepare any selected diblock copolymer.

For example, if PB-PEO diblock copolymers were selected, the synthesis of PB-PEO differs from the previous scheme by a single step, as would be understood by the practitioner. The step by which PB-OH is hydrogenated over palladium to form PEO-OH is omitted. Instead, the PB-OH intermediate is prepared, then it is reduced, for example, using potassium naphthalide, and converted to PB-PEO by the subsequent addition of ethylene oxide.

In yet another example, triblock copolymers having a PEO end group can also form polymersomes using similar techniques. Various combinations are possible comprising, e.g., polyethylene, polyethylethylene, polystyrene, polybutadiene, and the

like. For example, a polystyrene (PS)-PB-PEO polymer can be prepared by the sequential addition of styrene and butadiene in cyclohexane with hydroxyl functionalization, re-initiation and polymerization. PB-PEE-PEO results from the two-step polymerization of butadiene, first in cyclohexane, then in the presence of THF, hydrolyl functionalization, selective catalytic hydrogenation of the 1.2 PB units, and the addition of the PEO block.

A plethora of molecular variables can be altered with these illustrative polymers, hence a wide variety of material properties are available for the preparation of the polymersomes. ABC triblocks can range from molecular weights of 3,000 to at least 30,000 g/mol. Hydrophilic compositions should range from 20-50 percent in volume fraction, which will favor vesicle formation. The molecular weights must be high enough to ensure hydrophobic block segregation to the membrane core. The Flory interaction parameter between water and the chosen hydrophobic block should be high enough to ensure said segregation. Symmetry can range from symmetric ABC triblock copolymers (where A and C are of the same molecular weight) to highly asymmetric triblock copolymers (where, for example, the C block is small, and the A and B blocks are of equal length).

The polymersomes are preferably based on A PBd - PEO copolymer. Alternative polymers include poly(hexyl methacrylate)-block-poly[2-(dimethylamino)ethyl methacrylate] (PHMA-PDMA), poly(hexyl methacrylate)-block-poly(methacrylic acid) (PHMA-PMAA), poly(butyl methacrylate)-block-poly(methacrylic acid) (PBMA-PMAA), poly(ethylene oxide)-block-poly(hexyl methacrylate) (PEO-PHMA), poly(butyl methacrylate)-block-poly[2-(dimethylamino)ethyl methacrylate (PBMA-PDMA), poly(hexyl methacrylate)-block-poly[2-(dimethylamino)ethyl methacrylate (PHMA-PDMA), poly(butyl methacrylate)-block-Poly(ethylene oxide) (PBMA-PEO).

Generally (following synthesis) such a polymer is used to form polymersomes (vesicles).

Examples

Synthetic procedure for the formation of poly(glycerol methacrylate)-b-poly(hydroxypropyl methacrylate) (PGMA-PHPMA) polymersomes

$PGMA_{55}$ (8800 g/mol) macro-Chain Transfer Agent (macro-CTA) was synthesised by RAFT polymerisation using 2-cyano-2-propylbenzodithioate as the Chain Transfer Agent (CTA).

$PGMA_{55}$-$PHPMA_{330}$ diblock copolymers were synthesised by RAFT polymerisation using $PGMA_{55}$ as the macro-CTA.

In a typical synthetic procedure to prepare $PGMA_{55}$-$PHPMA_{330}$ polymersomes, $PGMA_{55}$ macro-CTA (0.1 g, 0.01136 mmol) and hydroxypropyl methacrylate (HPMA, 0.54 g, 3.75 mmol, 330 equivalents vs. Macro-CTA) were degassed under nitrogen flow in a 25 mL round bottom flask fitted with a magnetic stirrer bar. After 15 min, the radical initiator 4,4'-azobis(4-cyanopentanoic acid) (ACVA, 1.5 mg, 0.0053 mmol, 0.5 equivalent vs. Macro-CTA) was introduced in the reactor and flush with nitrogen during 5 min. Degassed and deionised water (6.4 mL, solid content 10 wt/V %) was then introduced in the reactor and bubbled with nitrogen during less than 5 min. The reactor was finally placed in a 70 °C oil bath. The reaction was left under stirring at 70 °C during 4 hours.

After reaction, a small amount of the polymersomes dispersion was diluted 50 times (solid content 0.2 wt/V %) and analysed by Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM).

Synthetic procedure for the formation of poly(glycerol methacrylate)-b-poly(hydroxypropyl methacrylate) (PGMA-PHPMA) polymersomes and the encapsulation of poly(ethylene glycol) 5000 g/mol (PEG 5K).

$PGMA_{55}$ (8800 g/mol) macro-Chain Transfer Agent (macro-CTA) was synthesised by RAFT polymerisation using 2-cyano-2-propylbenzodithioate as the Chain Transfer Agent (CTA).

$PGMA_{55}$-$PHPMA_{330}$ diblock copolymers were synthesised by RAFT polymerisation using $PGMA_{55}$ as the macro-CTA.

In a typical synthetic procedure to prepare $PGMA_{55}$-$PHPMA_{330}$ polymersomes and to encapsulate PEG 5K, $PGMA_{55}$ macro-CTA (0.1 g, 0.01136 mmol), hydroxypropyl methacrylate (HPMA, 0.54 g, 3.75 mmol, 330 equivalents vs. Macro-CTA) and PEG 5K (64 mg, 10 wt/wt % vs. Macro-CTA and HPMA) were degassed under nitrogen flow in a 25 mL round bottom flask fitted with a magnetic stirrer bar. After 15 min, the radical initiator 4,4'-azobis(4-cyanopentanoic acid) (ACVA, 1.5 mg, 0.0053 mmol, 0.5 equivalent vs. Macro-CTA) was introduced in the reactor and flush with nitrogen during 10 min. Degassed and deionised water (6.4 mL, solid content 10 wt/V %) was then introduced in the reactor and bubbled with nitrogen during less than 5 min. The reactor was finally placed in a 70 °C oil bath. The reaction was left under stirring at 70 °C during 4 hours. The reaction was stopped by allowing air inside the reactor and cooling the dispersion down to room temperature.

After reaction, a small amount of the polymersomes dispersion was diluted 50 times (solid content 0.2 wt/V %) and analysed by

Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM).

A part of the dispersion was dialysed against water during one week changing the water regularly (Membrane Cut-Off: 300 kDa, supplier "equivalent porosity": 20 nm).

The resulting dialysed dispersion was freeze-dried and analysed by Gel Permeation Chromatography (GPC, eluent: DMF at 60 °C, RI detector, PMMA standard calibration). The result was compared to a sample of the initial dispersion prepared before dialysis.

The GPC trace of the sample after dialysis revealed the presence of PEG 5K trapped within the polymersomes.

Control experiments were performed to prove that the 300 kDa membrane is perfectly permeable to the PEG 5K: A solution of PEG 5K in water was dialysed against water during one week, the resulting "solution" was then freeze-dried and finally analysed by NMR and mass difference. No remaining PEG 5K was noticeable.

CLAIMS

1. A method of preparing a composition comprising an active agent which is at least partially enclosed in a polymersome in a liquid formulation comprising admixing the active agent, the agents required for forming the polymersome and a liquid formulation, and allowing / causing polymersome formation.

2. A method of preparing a composition comprising an active agent which is at least partially enclosed in a polymersome in an aqueous liquid formulation comprising admixing the active agent, the agents required for forming the polymersome and an aqueous liquid formulation, and allowing / causing polymersome formation.

3 A method of preparing a composition comprising an active agent which is at least partially enclosed in a polymersome in an aqueous liquid formulation comprising admixing the active agent to be encapsulated the monomers to form the second block, the Macro CTA and the aqueous media in a single vessel to directly form a polymersome containing at least partially encapsulated active in the said vessel.

4. A method according to claim 1, 2 or 3, wherein the polymersome is a vesicle formed from an amphilic di-block copolymer, e.g. an admixture of polybutadiene (PBd) and polyethylene oxide (PEO) copolymers.

5. A method according to claim 1, 2 or 3, wherein the polymersome comprises PGMA-PHPMA.

6. A method according to any one of the preceding claims, wherein the concentration of polymersome is 0.5-50% by weight, more preferably from 5-20% by weight.

7. A method of delivering an active agent to a locus using a polymersome containing composition, wherein the polymersome containing active is produced in accordance with claim 1.

8. A method according to claim 7, wherein the disruption mechanism is a chemical and / or mechanical disruption.

9. A method according to claim 7, wherein disruption mechanisms include the application of mechanical shear and / or change in osmotic potential.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2012/050783

A. CLASSIFICATION OF SUBJECT MATTER
INV. C08F293/00 C08L53/00 C11D3/37
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)
C08F C08L C11D

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 2007/075502 A2 (UNIV PENNSYLVANIA [US]; QIN SHUHUI [US]; YANG SHU [US]; DISCHER DENNIS) 5 July 2007 (2007-07-05) page 2, line 28 - page 3, line 15; claims 10,18 page 4, line 9 - line 19 page 9, line 14 - line 20 page 11, line 11 - page 12, line 7 page 15, line 27 - line 32 page 16, line 14 - page 17, line 2; examples	1,2,4-9
X	US 2005/003016 A1 (DISCHER DENNIS E [US] ET AL) 6 January 2005 (2005-01-06) claims 1,18; examples	1,2,4-9

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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

"E" earlier application or patent but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 June 2012	26/06/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Iraegui Retolaza, E

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2012/050783

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 3(completely); 4-6(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 3(completely); 4-6(partially)

Independent claim 3 is open to objection under Article 6 PCT, clarity. The claim refers to a second block and to a Macro CTA wherein it is nos specified which block and CTA could be meant. The claim is so unclear that no meaningful search can be carried out. No search can be carried out concerning the subject-matter of claims 4 to 6 as far as dependent on claim 3.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2012/050783

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2011/144921 A2 (RECKITT & COLMAN OVERSEAS [GB]; BOWN GAVIN [FR]; CLAYTON CARL [GB]; MC) 24 November 2011 (2011-11-24) page 4, line 24 - page 5, line 2 page 21, line 8 - line 25 page 23, line 15 - page 24, line 2 page 24, line 17 - page 26, line 21; claims	1,2,4-9
X	US 2008/181939 A1 (DISCHER DENNIS E [US] ET AL) 31 July 2008 (2008-07-31) claim 15	1,4-9
X,P	WO 2011/109512 A1 (VINDICO NANOBIO TECHNOLOGY INC [US]; OSTERTAG ERIC M [US]; TUMEH PAUL) 9 September 2011 (2011-09-09) the whole document	1,4-6

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2012/050783

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007075502 A2	05-07-2007	US 2009220614 A1	03-09-2009
		WO 2007075502 A2	05-07-2007
US 2005003016 A1	06-01-2005	NONE	
WO 2011144921 A2	24-11-2011	NONE	
US 2008181939 A1	31-07-2008	NONE	
WO 2011109512 A1	09-09-2011	NONE	