Abstract:
The present invention deals with a new organogel formulation, comprising lecithin, water, ethanol and acylglycerols. Said organogel formulation can be used for therapeutical purposes, both per se and as matrix for a pharmaceutically or veterinary active agent. Said organogel formulation can also be used in the treatment of dermatological affections or as a matrix for cosmetic or personal care substances.
Organogel formulation and uses thereof

The present invention deals with a new organogel formulation, comprising lecithin, water, ethanol and at least one acylglycerol. Said organogel formulation can be used for therapeutical purposes, both per se and as matrix for a pharmaceutically or veterinary active agent. Said organogel formulation can also be used in the treatment of dermatological affections or as a matrix for cosmetic or personal care substances.

Background of the invention

Topical administration of drugs, in order to achieve optimal cutaneous and percutaneous drug delivery, is a favorite subject to study nowadays because of various advantages such as ease of administration and delivery benefits. Formulations in gel form are particularly appropriate for topical administration route.

Lecithin organogels have been for instance studied as vehicles for topical drug delivery (see for instance, Kumar et al. AAPS PharmSciTech 2005, 6(2), E298-E310). Said organogels are formed by gelation of a binary system comprising lecithin and an apolar solvent, for instance oil, when said system is contacted with traces of a polar solvent, for instance water. According to the physical interpretation presented in publications, the obtained organogel is a jelly-like structure that consists of three-dimensional networks of entangled reverse cylindrical micelles, which immobilize the continuous phase and thus convert from liquid to viscous gel.

However, several publications point that said organogels can only be obtained when the lecithin contains more than 95% phosphatidylcholine and is free from fat as well as moisture (for instance Kumar et al., see above, or Raut et al. Acta Pharmacoeutica Sinica B 2012, 2(1), 8-15). As the organogels comprise a substantial amount of lecithin (the molar ratio of water to lecithin in organogels is typically 2:10), the need of highly pure lecithin can be an issue, in particular regarding the industrial development of lecithin organogels, because it is expensive and difficult to obtain in large quantities. Lecithin plays the role of gelator molecules in said ternary systems.

In addition, when such organogels are used as a vehicle for the delivery of hydrophilic active agents, the amount of active agent that can be incorporated is limited by the
amount of water comprised in the system. Actually, when the water amount is increased in said organogels, the 3-dimensional network collapses over a certain n ratio, wherein n ratio is the molar ratio of water to lecithin.

In this context, the Applicant surprisingly discovered that organogels can be formed with the combination of lecithin, water, ethanol and at least one acylglycerol. The acylglycerol preferably acts as a gel-forming agent, like lecithin. The use of said acylglycerol affords the possibility to reduce the amount of expensive high-purity lecithin to be used to form the organogels. In addition, organogels according to the invention may comprise relatively high amounts of water, thus affording the possibility to incorporate higher amounts of hydrophilic compounds, such as hydrophilic active agents.

**Summary of the invention**

A first object of the invention is an organogel formulation, wherein said organogel comprises lecithin, water, ethanol and a mixture of acylglycerols of formula (I) as defined below.

Another object of the present invention is an organogel formulation comprising:
- from 5 to 23 wt% water,
- from 0.01 to 9.5 wt% ethanol,
- from 25 to 50 wt% lecithin, and
- from 30 to 49 wt% acylglycerol, relative to the total weight of the organogel.

Another object of the invention is an organogel formulation comprising lecithin, water, ethanol and at least one acylglycerol, for use as a medicament.

Another object of the invention is an organogel formulation comprising lecithin, water, ethanol and at least one acylglycerol, and further comprising at least one active agent.
**Brief description of the figures**

Figure 1: Photograph of an organogel sample and a liquid sample

Figure 2: Polarized microscopy micrographs of samples 1 (a), 2 (b), 3 (c), 4 (d), 5 (e), 6 (f) and 7 (g)

Figure 3: Rheological characterization of samples 1 (a), 2 (●), 3 (■) and 4 (X) (b), and of samples 5 (+), 6 (X) and 7 (★ Xc)

Figure 4: SAXS characterization of samples 2 (●), 3 (■) and 4 (A) (a), and of samples 5 (■) and 7 (★) (b).

**Detailed description of the invention**

A first object of the invention is an organogel formulation, wherein said organogel comprises lecithin, water, ethanol and a mixture of acylglycerols.

In the present invention, the terms "organogel" or "organogel formulation" represent a semi-solid, jelly-like material (gel), for instance with a viscoelastic behavior. The organogel according to the invention presents rheological characteristics different from those of a Newtonian liquid. Preferably, the yield stress of an organogel formulation according to the invention is strictly superior to the yield stress of a Newtonian liquid (that is 0 Pa under conditions as described below). The yield stress is the stress level at which the gel ceases to behave elastically.

As exposed in the example section, the rheological characterization of the organogels according to the invention is preferably performed using TA instrument Rheometer (AR 2000 EX). A cone plate with a diameter of 4cm and 6cm and an angle of 2° and 1.1° respectively is used. Temperature is preferably between around 20 and around 25°C.

The organogel formulations according to the invention can be prepared by classical formulation methods used for preparing organogels. One of ordinary skill in the art is able to determine the appropriate experimental conditions (such as stirring rate and/or
temperature for instance) for forming the organogel by mixing the different components.

Acylglycerols are amphiphilic compounds and can thus cooperate with lecithin to form stable structures in the organogel. Said cooperation favors the gelation of the composition comprising lecithin, water, ethanol and a mixture of acylglycerols according to the invention. In addition, acylglycerols are gel-forming agents. They can consequently be implied in favoring gelation of the composition and/or stabilizing said organogel.

The organogel formulation according to the invention does not comprise, as compulsory components for obtaining the organogel, any apolar solvent like alkanes, alkenes or mixtures thereof. Preferably, the organogel formulation according to the invention does not comprise any polymer, such as poloxamers.

In an embodiment, the organogel formulation according to the invention comprises:
- from 5 to 23 wt% water,
- from 0.01 to 9.5 wt% ethanol,
- from 25 to 50 wt% lecithin, and
- from 30 to 49 wt% acylglycerols, preferably 30 to 46 wt%, relative to the total weight of the organogel formulation.

Components of the organogel formulation

> Acylglycerols

Acylglycerols used in the organogel formulation according to the invention can be isolated from the majority of animals, and more preferably plants. Acylglycerols used in the organogel formulation according to the invention include mono-, di- and/or tri-acylglycerols of the following formula (I):
- $R_1$ is an acyl residue of a linear or branched unsaturated fatty acid having between 14 and 24 carbon atoms;

- $R_2$ is an acyl residue of a linear or branched unsaturated fatty acid having between 2 and 18 carbon atoms, or a hydrogen atom;

- $R_3$ is an acyl residue of a linear or branched unsaturated fatty acid having between 14 and 24 carbon atoms, or a hydrogen atom.

According to a particular embodiment, $R_1$ or $R_3$, preferably only one of $R_1$ and $R_3$, in particular only $R_1$, represents an acyl residue of oleic acid (C18:1[cis]-9).

According to a particular aspect, $R_2$ is an acyl residue of a linear or branched unsaturated fatty acid having between 2 and 18 carbon atoms, and preferably has 18 carbon atoms, preferably $R_2$ is an oleic acid residue (oleoyl group), one of its positional isomers with respect to the double bond (cis-6,7,9,11 and 13) or one of its iso-branched isomers.

According to another particular aspect, $R_1$ represents an oleoyl group.

According to another particular aspect, $R_3$ is a hydrogen atom.

As a general rule, oil containing a high concentration of oleic acid will be chosen as a useful source of acylglycerols according to the invention. Such oil usually contains a high proportion of acylglycerols useful according to the invention.

According to a particular aspect of the invention, the preferred acylglycerols are glycerol 1-monooleate and glycerol 1,2-dioleate.

A certain number of them, and more particularly those which are found to be the most active in the applications sought after, are also available commercially. For instance, glycerol monooleate 40 contains about 32 to 52% of monoacylglycerol, 30 to 50% of diacylglycerol, 5 to 20% of triacylglycerol and is pharmaceutically accepted (European Pharmacopeia (8th Edition), USP 25/NF20, and Japanese Standard of food Additives).
Such product is for instance commercially available by Gattefosse Company under the name Peceol®. In particular, Peceol® may comprise around 45.3 wt% of monoacyl glycerol, around 44.5 wt% of diacylglycerol and around 8.6 wt% of triacyl glycerol (the acyl fraction of Peceol® is mainly made of oleoyl - usually around 80% of the acyl residue is oleoyl fraction).

According to a particular aspect of the invention, the acylglycerol comprised in the composition of the invention is a mixture of acylglycerols, of formula (I) as defined above, and more specifically said mixture comprises monoacylglycerol and diacylglycerol, of formula (I), and optionally triacylglycerol of formula (I), as defined above. In a particular embodiment, the mixture comprises more than 25% of monoacylglycerol, based on the total weight of said mixture.

More specifically, said mixture comprises 32 to 52% of monoacylglycerol, 30 to 50% of diacylglycerol, and 5 to 20% of triacylglycerol, based on the total weight of said mixture.

The acylglycerols are preferably incorporated or comprised in the organogel formulation in an amount by weight ranging from 23 g to 49 g, more preferably from 30 g to 46 g, with respect to 100 g of the total weight of the organogel formulation according to the invention.

According to the present description, the weight of acylglycerol corresponds to the total weight of the mixture usually containing acylglycerols, or a mixture of acylglycerols, with glycerol and fatty acids derived from said acylglycerol(s), such as Peceol® described above.

Acylglycerols preferably act as gel-forming agents in the organogel formulations according to the invention.

Acylglycerols are natural compounds, and may be extracted and/or derived from vegetable sources. Their use is thus favoured in terms of biocompatibility and environmental concerns when compared to synthetic compounds.
> Lecithin

In the present invention, the term "lecithin" designates phosphatidylcholine. Phosphatidylcholine is also known as 1,2-diacyl-glycero-3-phosphocholine or PtdCho. Phosphatidylcholine is formed from a choline, a phosphate group, a glycerol and two fatty acids. It is actually a group of molecules, wherein the fatty acid compositions varies from one molecule to another. Phosphatidylcholine may be obtained from commercial lecithin that contains phosphatidylcholine in weight concentrations of 20 to 98%. The lecithin preferably used in the organogel formulations according to the invention is Epikuron 200® and contains phosphatidylcholine at a concentration of more than 90%. Preferably, the lecithin used in the organogel formulations according to the invention comprises more than 93% phosphatidylcholine.

The weight ratio lecithin/acylglycerol in organogel formulations according to the invention is preferably from 0.51 to 2.20, preferably 0.51 to 1.64.

The lecithin is preferably incorporated or comprised in the organogel formulation in an amount by weight ranging from 15 g to 50 g, preferably from 25 to 50 g, with respect to 100 g of the total weight of the organogel formulation according to the invention.

> Water

The water useful for the preparation of the organogel formulation according to the invention is preferably purified water.

The weight ratio lecithin/water in organogel formulations according to the invention is preferably from 1.0 to 10.0.

Water is preferably incorporated or comprised in the organogel formulation in an amount by weight ranging from 5 g to 50 g, preferably from 5 to 23 g with respect to 100 g of the total weight of the organogel formulation according to the invention.

One of ordinary skill in the art will adapt the amount of lecithin, ethanol and/or acylglycerol in the organogel formulations to the desired properties for said organogel. For instance, the amount of lecithin and/or acylglycerol will be adapted to the desired amount of water in the organogel.

In an embodiment, the molar ratio water/(surface active agents), wherein the surface active agents are lecithin, diacylglycerols and monoacylglycerols, is at least equal to 6.5.
Ethanol

Ethanol is preferably incorporated or comprised in the organogel formulation in an amount by weight ranging from 0.01 to 9.5 g, preferably from 6 to 9 g with respect to 100 g of the total weight of the organogel formulation according to the invention.

The presence of ethanol is useful to make the organogel formulation more spreadable. It is also useful as permeation enhancer, for instance when the organogel formulation comprising an active agent is applied topically.

Other components

The organogel formulation according to the invention may comprise additional components. As examples of additional components, one can cite sterols and alcohols different from ethanol.

In a preferred embodiment, the organogel formulation does not comprise liposomes.

Sterol

The organogel formulation according to the invention may comprise at least one sterol, preferably natural sterol, such as cholesterol or phytosterol (vegetable sterols). Sitosterol and cholesterol are the preferred sterols that can be present in an organogel formulation according to the invention. Preferably, the organogel comprises sitosterol.

Sitosterol and cholesterol are commercially available. More particularly, commercial sitosterol which is extracted from soya can be used. In such a product, the sitosterol generally represents from 50 to 80 % by weight of the product and is generally found in a mixture with campesterol and sitostanol in respective proportions in the order of 15% each. Commercial sitosterol which is extracted from a variety of pine called tall oil can also be used.

When a sterol is comprised in the organogel formulation according to the invention, the sterol is preferably incorporated or comprised in the organogel formulation in an amount by weight ranging from 0.825 g to 4.5 g, preferably from 2 g to 3 g, in particular around 2.5 g, with respect to 100 g of the total weight of the organogel formulation according to the invention.
o Alcohols

The organogel formulation according to the invention may comprise at least one alcohol in addition to ethanol as defined above. The alcohols that may be used according to the invention are preferably linear or branched mono-alcohols from C2 to C3. Examples of alcohols are 1-propanol, 2-propanol, 2-methyl-1-propanol, isopropanol, and any mixture thereof. Polyols that may be used according to the invention are preferably glycerol and propylene glycol. When an alcohol is present in the organogel formulation in addition to ethanol, it is preferably incorporated or comprised in the organogel formulation in an amount by weight ranging from 0.01 g to 10 g, preferably from 2 g to 9 g, in particular around 9 g, with respect to 100 g of the total weight of the organogel formulation according to the invention.

In a specific embodiment, the total amount of the alcohols comprised in the organogel formulation, including ethanol, is comprised between 6 g and 9 g, in particular around 9 g, with respect to 100 g of the total weight of the organogel formulation according to the invention.

The amounts of the components of the gel are defined with respect to the total weight of the organogel, in absence of active agent incorporated therein. If a great amount of an active agent is added to the gel, modifying substantially the total weight of the gel, the amounts of the components (apart from the active agent) may be out of the ranges defined above. Consequently, the amounts specified in the present description are the amounts (or %) of the components of the organogel formulation without any active agent, unless otherwise specified.

Use of the organogel formulation

An organogel formulation according to the invention may be used for therapeutical, more specifically dermatological, and/or cosmetic purposes.

An organogel formulation according to the invention may be used for human and/or animal, preferably mammal, subjects.

An object of the present invention is an organogel formulation according to the invention, for use as a medicament.
In an embodiment, the organogel formulation is used *per se* (i.e., without incorporation of any active agent, specifically pharmaceutically active agent) for a therapeutical purpose. Accordingly, the invention relates to a pharmaceutical composition comprising the organogel formulation as defined above, and optionally a pharmaceutically acceptable support.

In an embodiment, the organogel formulation according to the invention or the composition comprising the same is used in the field of cicatrisation and/or healing, more specifically skin cicatrisation and/or healing. For instance, the organogel formulation or the composition comprising the same may be used for improving and/or accelerating cicatrisation of a wound, a burn, an inflammation and/or a bedsore. In particular, the organogel formulation or the composition comprising the same according to the invention reduces the cicatrisation time of a wound, a burn, an inflammation and/or a bedsore, preferably a non-infected wound, burn, inflammation and/or bedsore.

In a particular embodiment, the organogel formulation or the composition comprising the same used for cicatrisation does not comprise any pharmaceutically active agent.

In another embodiment, the organogel formulation according to the invention further comprises at least one active agent, preferably at least one pharmaceutically or veterinary active agent. Accordingly, the invention relates to a pharmaceutical composition comprising the organogel formulation as defined above, at least one active agent, preferably at least one pharmaceutically or veterinary active agent, and optionally a pharmaceutically acceptable support.

Another object of the invention is thus an organogel formulation according to the invention or a composition comprising the same, further comprising at least one active agent, preferably pharmaceutically or veterinary active agent.

The term "pharmaceutically or veterinary active agent" refers in the present invention to any compound susceptible to have a prophylactic and/or therapeutical action, preferably in the course of the treatment of a pathology. The pharmaceutically active agent is more specifically hydrophilic.
Among pharmaceutically active agents that can be added to an organogel formulation according to the invention can be cited for instance metals, such as selenium, silver, copper, vanadium, manganese or zinc, or any pharmaceutically acceptable salt thereof, antalgics, analgesics, anesthetics, such as lidocaine chloride, alkaloids such as caffeine, anti-inflammatory compounds, anti-microbial compounds such as antibiotics, antivirals and antifungals, antiseptics, immunosuppressants, antihistamines, cytostatics, retinoids, antioxidants, peptides, polypeptides, proteins, neurotoxins such as botulinum toxin, polysaccharides, nucleic acids for gene therapy [DNA or RNA (more particularly RNAi) or fragments thereof], and dermatologically-active agents.

Another object of the invention is an organogel formulation according to the invention or a cosmetic composition comprising the same, further comprising at least one cosmetic or personal care substance. Preferably, the organogel that comprises at least one cosmetic or personal care substance does not comprise any pharmaceutically and/or veterinary active agent.

The term "cosmetic or personal care substance" refers for instance to components useful for shampoo, conditioner, hair gel, toothpaste, soap, skin treatments, shaving treatments, lotions, and may be for instance fragrances, skin-care additives, botanicals, astringents, moisturizers, emollients, make-up items, anti-cellulite agents, UV protectors, active agents against skin aging, or skin coloring substances.

The use of the organogel formulation as matrix for at least one active agent or cosmetic or personal care substance affords several advantages. First, the organogel formulation affords the possibility of sustained release of the active agent or cosmetic or personal care substance. It also allows the simultaneous delivery of several active ingredients and/or cosmetic or personal care substances over a prolonged period of time.

In addition, the use of said organogel formulation may improve the stability of the at least one active agent or cosmetic or personal care substance, preferably its in vivo stability. For instance, the use of the present organogel formulation as a matrix may
limit the enzymatic degradation of the at least one active agent or cosmetic or personal
care substance.

The organogel formulation according to the invention, *per se* or as a matrix for at least
one active agent or cosmetic or personal care substance, can be administered by any
appropriate route. Preferably, the organogel formulation or composition comprising the
same is administered by the topical, transdermal or transmucosal route. In a particular
embodiment, the organogel formulation or composition comprising the same is
administered topically onto the skin.

The organogel formulation according to the invention or the composition comprising
the same is advantageously dermo and/or muco-adhesive.

The organogel formulation according to the invention or the composition thereof
provides a comfortable feel when applied onto the skin.

The organogel formulation according to the invention is preferably highly
biocompatible, in particular at the cellular level.

In an embodiment, the organogel formulation according to the invention presents
improved properties for the restructuration and/or regeneration of biological materials
such as skin or cellular membranes.

In an embodiment, the use of the organogel formulation according to the invention for
the delivery of a pharmaceutically active agent increases the ability of said agent to
cross the skin and/or the cellular membranes.

The organogel formulation according to the invention may be used in the treatment of
any pathological condition and/or disease for which at least one of the active agents that
can be incorporated in the organogel formulation has a beneficial effect. This effect can
be for instance a prophylactic and/or therapeutic treatment, a slow-down of the
progression of the disease, or the reduction of at least one symptom of the disease.
The organogel formulation according to the invention may be used in the treatment of dermatological affections, for instance acne, eczema, fungal, viral or bacterial affections, psoriasis or pruritus.

The organogel formulation according to the invention may be used for cosmetics and/or personal care.

According to the invention, the term "comprise(s)" or "comprising" can be generally interpreted such that all of the specifically mentioned features and any optional, additional and unspecified features are included; it can also be interpreted more specifically as the expression "consisting of where only the specified features are included, unless otherwise specified.

The present invention includes the specific embodiments as described above and any combination thereof.

In the present invention, the percentage values are weight percentage values, unless otherwise indicated.

The term "around" or "about" a value refers to a range between +10% of the value.

The following examples are provided only as illustrative, and not limitative, of the invention.

**Examples**

**Example 1: Preparation of the samples**

For preparing samples, commercially available lecithin, containing 94.5% of phosphatidylcholine, was dissolved in absolute ethanol by magnetic stirring at room temperature at 300 r/min. Phystosterol, containing 78.6% of beta-sitosterol, was added to the mixture and stirred in the same conditions. Peceol ® was added thereto and magnetic stirring was carried out at 700 r/min at 37°C to form an oil mixture. The lipid mixture was ready for use immediately and contacted to purified water at room
temperature and stirred at 700 r/min. If necessary, bubbles could be removed by heating samples at 50°C. The samples were then stored at least over night at room temperature before further characterization in order to determine visually texture and phase boundary.

Table 1 shows the quantities (g) and the % of individual components in the different samples.

<table>
<thead>
<tr>
<th>Sample 1</th>
<th>Lecithin (g)</th>
<th>Ethanol (g)</th>
<th>Phytosterol (g)</th>
<th>Peceol® (g)</th>
<th>Water (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.41</td>
<td>0.85</td>
<td>0.23</td>
<td>5.78</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>9.0</td>
<td>2.5</td>
<td>61.5</td>
<td>12.0</td>
</tr>
<tr>
<td>Sample 2</td>
<td>3.20</td>
<td>0.86</td>
<td>0.23</td>
<td>3.71</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>34.0</td>
<td>9.1</td>
<td>2.5</td>
<td>39.4</td>
<td>15.0</td>
</tr>
<tr>
<td>Sample 3</td>
<td>3.76</td>
<td>0.85</td>
<td>0.23</td>
<td>3.15</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>40.0</td>
<td>9.0</td>
<td>2.5</td>
<td>33.5</td>
<td>15.0</td>
</tr>
<tr>
<td>Sample 4</td>
<td>4.70</td>
<td>0.85</td>
<td>0.23</td>
<td>2.22</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>50.0</td>
<td>9.0</td>
<td>2.5</td>
<td>23.5</td>
<td>15.0</td>
</tr>
<tr>
<td>Sample 5</td>
<td>1.41</td>
<td>0.85</td>
<td>0.23</td>
<td>3.16</td>
<td>3.76</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>9.0</td>
<td>2.5</td>
<td>33.5</td>
<td>40.0</td>
</tr>
<tr>
<td>Sample 6</td>
<td>2.25</td>
<td>1.36</td>
<td>0.38</td>
<td>4.27</td>
<td>6.76</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>9.0</td>
<td>2.5</td>
<td>28.4</td>
<td>45.0</td>
</tr>
<tr>
<td>Sample 7</td>
<td>1.41</td>
<td>0.85</td>
<td>0.23</td>
<td>2.22</td>
<td>4.71</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>9.0</td>
<td>2.5</td>
<td>23.5</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Table 1

Table 2 below presents the water/lecithin molar ratio, and the water/(surface active agents) molar ratio for each sample of table 1. The surface active agents are lecithin, and glycerol monooleate and glycerol dioleate comprised in Peceol®. The mean molecular weight of glycerol monooleate and glycerol dioleate is used for calculating said ratio.

<table>
<thead>
<tr>
<th>Sample</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water/lecithin</td>
<td>33.8</td>
<td>18.6</td>
<td>15.8</td>
<td>12.7</td>
<td>112.6</td>
<td>127.4</td>
<td>141.0</td>
</tr>
<tr>
<td>Water/(surface active agents)</td>
<td>4.6</td>
<td>6.6</td>
<td>6.8</td>
<td>7.3</td>
<td>24.9</td>
<td>32.0</td>
<td>40.6</td>
</tr>
</tbody>
</table>

Table 2

Figure 1 presents comparative sample 1 (right side) and sample 2. It is clear that sample 2 is an organogel, when sample 1 is a liquid.
Example 2: Characterization of the samples

2a. Polarized microscopy

Materials and methods:
Polarizing light microscopy can be used to differentiate microemulsion (isotropic liquid) to liquid crystalline phases (LC). LC is easily distinguished by the birefringence displayed with the polarized light. Samples were analyzed under a polarized light microscope (Axiolab, Zeiss) at 10x magnification, the microscope is attached to a canon A620 camera, slides were examined at ambient temperature (25°C). A drop of sample was placed between a coverslip and a glass slide and then examined under cross-polarized light.

Results:
Polarized microscopy pictures are provided on figure 2 for samples 1, 2, 3, 4, 5, 6 and 7. Sample 1 is not birefringent under polarized light, which is characteristic of an isotropic medium, in the present case an isotropic liquid. Conversely, samples 2, 3, 4, 5, 6 and 7 are highly birefringent under polarized light, which is characteristic of an anisotropic medium, in the present case liquid crystalline phases.

2b. Rheological characterization (figure 3)

Materials and methods:
Rheology measurements were performed using TA instrument Rheometer (AR 2000 EX). A cone plate with a diameter of 4cm and 6cm and an angle of 2° and 1.1° respectively was used. Temperature was maintained at 25 ± 0.1°C. Shear rate measurements were performed between 0.01 and 1000 s⁻¹. A sample volume of 1 ml was used.

Results:
Figure 3 presents the shear stress in function of the shear rate for samples 1, 2, 3, 4, 5, 6 and 7. Sample 1 exhibits a linear dependence of the shear stress as a function of shear rate, which is characteristic of a Newtonian liquid. Samples 2, 3, 4, 5, 6 and 7 exhibit a non-linear dependence of the shear stress as a function of shear rate, which is characteristic of a viscoelastic medium. This viscoelastic behavior with such yield stress values indicates higher order of structure of the system (i.e. liquid crystalline phase).

Table 3 below presents the viscosity (Pa.s) and yield stress (Pa) values for samples 2, 3, 4, 5, 6 and 7.
<table>
<thead>
<tr>
<th>Sample</th>
<th>Viscosity (Pa.s)</th>
<th>Yield stress (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>131</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>96</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>172</td>
<td>108</td>
</tr>
</tbody>
</table>

Table 3

Contrary to sample 1 (which has a Newtonian liquid behavior), organogel samples 2 to 7 present a viscoelastic behavior.

2c. SAXS (Small Angle X-ray Scattering) characterization (figure 4)

Materials and methods:

Scattering measurements were performed using the XENOCS instrument at Marcoule Institute for Separative Chemistry. The wavelength of the incident X-ray beam from Mo-radiation was \( \lambda = 0.71 \text{ Å} \). The distance from the sample to the detector was calibrated by silver behenate. The sample was sealed in a 1.0 mm capillary tube, and all measurements were performed at ambient temperature (25°C). Pre-analysis of data was performed using FIT2D software, taking into account the electronic background of the detector and the empty cell subtraction. The scattered intensities are expressed versus the magnitude of scattering vector \( Q = (4\pi/\lambda) \sin (q/2) \), where \( \lambda \) is the wavelength of incident radiation and \( q \) the scattering angle. Experimental resolution was \( DQ/Q = 0.05 \).

Results:

Figure 4 presents the SAXS spectra obtained for samples 2, 3 and 4 on one hand, and 5 and 7 on the other hand. Several sharp diffraction peaks are evidenced in the low angle X-ray region for all samples. These peaks are characteristic of liquid crystalline structure of the samples.
Example 3: Organogels comprising active agents

Organogels could be successfully obtained when adding caffeine, silver, copper, zinc, manganese or niflumic acid to formulations comprising lecithin, Peceol®, water, ethanol and beta-sitosterol. The details of the formulations are provided below:

> Copper, manganese and zinc

36.9 g of commercially available lecithin, containing 93.5% of phosphatidylcholine, was dissolved in 9.0 g of absolute ethanol by magnetic stirring at room temperature at 300 r/min. 2.5 g of phystosterol, containing 76.3% of beta-sitosterol, was added to the mixture and stirred in the same conditions. 36.5 g of Peceol® was added thereto and magnetic stirring was carried out at 700 r/min at 37°C to form an oil mixture. Solutions at 0.2 mg/ml of copper, manganese or zinc were prepared in purified water. 1.5 g of each metal solution were preheated at 37°C and mixed to 8.5 g of preheated oil mixture by vortexing few minutes to form samples at 0.03 mg/g. If necessary, bubbles could be removed by heating samples at 50°C.

Samples were then stored at least over night at room temperature before further characterization in order to determine visually texture and phase boundary.

Table 4 shows % of individual components in the different samples.

> Silver

37.5 g of commercially available lecithin, containing 93.5% of phosphatidylcholine, was dissolved in 11.3 g of absolute ethanol by magnetic stirring at room temperature at 300 r/min. 3.1 g of phystosterol, containing 76.3% of beta-sitosterol, was added to the mixture and stirred in the same conditions. 48.3 g of Peceol® was added thereto and magnetic stirring was carried out at 700 r/min at 37°C to form an oil mixture. Solution at 0.5 mg/ml of silver was prepared in purified water. 2.0 g of this solution was preheated at 37°C and mixed to 8.0 g of the oil mixture by vortexing few minutes to form sample at 0.1 mg/g. If necessary, bubbles could be removed by heating samples at 50°C.

The samples were then stored at least over night at room temperature before further characterization in order to determine visually texture and phase boundary.

Table 4 shows % of individual components in the different samples.
> **Caffeine**

29.9 g of commercially available lecithin, containing 93.5% of phosphatidylcholine, was dissolved in 9.2 g of absolute ethanol by magnetic stirring at room temperature at 300 r/min. 2.5 g of phystosterol, containing 76.3% of beta-sitosterol, was added to the mixture and stirred in the same conditions. 38.5 g of Peceol® was added thereto and magnetic stirring was carried out at 700 r/min at 37°C to form an oil mixture. Solution at 20.0 mg/ml of caffeine was prepared in purified water. 1.0 g of this solution was preheated at 37°C and mixed to 4.0 g of the oil mixture by vortexing few minutes to form sample at 4.0 mg/g. If necessary, bubbles could be removed by heating samples at 50°C.

Samples were then stored at least over night at room temperature before further characterization in order to determine visually texture and phase boundary.

Table 4 shows % of individual components in the different samples.

> **Niflumic acid**

29.9 g of commercially available lecithin, containing 93.5% of phosphatidylcholine, was dissolved in 9.2 g of absolute ethanol by magnetic stirring at room temperature at 300 r/min. 2.5 g of phystosterol, containing 76.3% of beta-sitosterol, was added to the mixture and stirred in the same conditions. 38.5 g of Peceol® was added thereto and magnetic stirring was carried out at 700 r/min at 37°C to form an oil mixture. 16.6 mg of niflumic acid was added to 4.0 g of the oil mixture. 1g of preheated purified water was added by vortexing few minutes to form sample at 3.3 mg/g. If necessary, bubbles could be removed by heating samples at 50°C.

Samples were then stored at least over night at room temperature before further characterization in order to determine visually texture and phase boundary.

Table 4 shows % of individual components in the different samples.
<table>
<thead>
<tr>
<th>Sample</th>
<th>API (%</th>
<th>Lecithin (%)</th>
<th>Phytosterol (%)</th>
<th>Ethanol (%)</th>
<th>Pecol (%)</th>
<th>Water (%)</th>
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<tbody>
<tr>
<td>8</td>
<td>Copper (0.003)</td>
<td>36.7</td>
<td>2.5</td>
<td>9.0</td>
<td>36.3</td>
<td>15.4</td>
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<tr>
<td>9</td>
<td>Manganese (0.003)</td>
<td>36.9</td>
<td>2.5</td>
<td>9.0</td>
<td>36.5</td>
<td>15.0</td>
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<tr>
<td>10</td>
<td>Zinc (0.003)</td>
<td>36.8</td>
<td>2.5</td>
<td>9.0</td>
<td>36.5</td>
<td>15.1</td>
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<tr>
<td>11</td>
<td>Silver (0.010)</td>
<td>29.9</td>
<td>2.5</td>
<td>9.0</td>
<td>38.5</td>
<td>20.1</td>
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<tr>
<td>12</td>
<td>Caffeine (0.40)</td>
<td>29.9</td>
<td>2.5</td>
<td>9.2</td>
<td>38.5</td>
<td>19.8</td>
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<tr>
<td>13</td>
<td>Niflumic acid (0.33)</td>
<td>29.8</td>
<td>2.5</td>
<td>9.2</td>
<td>38.3</td>
<td>19.9</td>
</tr>
</tbody>
</table>

Table 4
CLAIMS

1. An organogel formulation, wherein said organogel comprises lecithin, water, ethanol and a mixture of acylglycerols of formula (I):

\[
\begin{align*}
\text{CH}_2\text{OR}_1 \\
\text{CH}_2\text{OR}_2 \\
\text{CH}_3\text{OR}_3 \\
\end{align*}
\]

(1)

wherein
- \( \text{R}_1 \) is an acyl residue of a linear or branched unsaturated fatty acid having between 14 and 24 carbon atoms;
- \( \text{R}_2 \) is an acyl residue of a linear or branched unsaturated fatty acid having between 2 and 18 carbon atoms, or a hydrogen atom;
- \( \text{R}_3 \) is an acyl residue of a linear or branched unsaturated fatty acid having between 14 and 24 carbon atoms, or a hydrogen atom,

wherein said mixture comprises monoacylglycerol and diacylglycerol, of formula (I), and optionally triacylglycerol.

2. The organogel formulation according to claim 1, wherein the organogel further comprises at least one sterol, preferably sitosterol.

3. The organogel formulation according to claim 1 or 2, comprising:

- from 5 to 23 wt% water,
- from 0.01 to 9.5 wt% ethanol,
- from 25 to 50 wt% lecithin, and
- from 30 to 49 wt% acylglycerols, relative to the total weight of the organogel.

4. The organogel formulation according to claim 3, wherein the organogel comprises from 6 to 9wt% ethanol, in particular around 9wt% ethanol.
5. The organogel formulation according to claim 3 or 4, wherein the organogel further comprises sitosterol, preferably from 2 to 3wt% sitosterol, in particular around 2.5wt% sitosterol.

6. The organogel formulation according to anyone of claims 1 to 5, wherein the lecithin/acylglycerols weight ratio is between 0.51 and 2.20, and/or the lecithin/water weight ratio is between 1.0 and 10.0.

7. The organogel formulation according to anyone of claims 1 to 6, wherein the mixture comprises 32 to 52% of monoacylglycerol, 30 to 50% of diacylglycerol, and 5 to 20% of triacylglycerol, based on the total weight of said mixture.

8. The organogel formulation according to anyone of claims 1 to 7, further comprising at least one active agent.

9. An organogel formulation as defined in anyone of claims 1 to 8, for use as a medicament.

10. The organogel formulation for use according to claim 9, wherein the organogel is administered by topical, transmucosal or transdermal administration.

11. An organogel formulation as defined in anyone of claims 1 to 8, for use in the treatment of a dermatological affection.

12. An organogel formulation as defined in anyone of claims 1 to 8, for use in improving and/or accelerating cicatrisation of a wound, a burn, an inflammation and/or a bedsore.

13. An organogel formulation as defined in claim 8, for use in the treatment of a pathology for which at least one of the active agents has a beneficial effect.

14. The organogel formulation according to anyone of claims 1 to 7, further comprising at least one cosmetic or personal care substance.
15. Use of an organogel formulation as defined in anyone of claims 1 to 7 or 15 in cosmetics and/or personal care.
Figure 1
Figure 4
# INTERNATIONAL SEARCH REPORT

**International application No**

PCT/EP2014/072657

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**A. CLASSIFICATION OF SUBJECT MATTER**


According to International Patent Classification (IPC) into both national classification and IPC

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**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

EPO-Internal, BIOSIS, CHEMABS Data, EMBASE, WPI Data

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>wo 2006/075123 A1 (CAMURUS AB [SE]); GODDARD CHRISTOPHER [GB]; JOABSSON FREDRIK [SE]; LIND) 20 July 2006 (2006-07-20) examples page 10, line 15 - line 22</td>
<td>1, 6, 8-15</td>
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<td>X</td>
<td>wo 2011/075623 A1 (LATITUDE PHARMACEUTICALS INC [US]; CHEN ANDREW XIAN [US]; CHEN HAI LIAN) 23 June 2011 (2011-06-23) examples</td>
<td>1, 2, 6, 8, 9</td>
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<td>X</td>
<td>wo 2011/117333 A2 (MEDESIS PHARMA [FR]; MAUREL JEAN-CLAUDE [FR]) 29 September 2011 (2011-09-29) examples page 6, line 23 - page 8, line 9</td>
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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* 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 wherein may throw doubts on priority claim(s) on 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

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Date of the actual completion of the international search

20 January 2015

Date of mailing of the international search report

28/01/2015

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Kol Imannsberger, M

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Form PCT/ISA/210 (second sheet) (April 2005)
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<td>A</td>
<td>LI-JUAN HAN ET AL: &quot;Rheological properties of organogels developed by sitosterol and lecithin&quot;, FOOD RESEARCH INTERNATIONAL, vol. 53, no. 1, 1 August 2013 (2013-08-01), pages 42-48, XP055101374, ISSN: 0963-9969, DOI: 10.1016/j.foodres.2013.03.039 the whole document</td>
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<td>MURDAN SUDAXSHINA: &quot;ORGANOGELS IN DRUG DELIVERY&quot;, EXPERT OPINION ON DRUG DELIVERY, INFORMA HEALTHCARE, GB, vol. 2, no. 3, 1 January 2005 (2005-01-01), pages 489-505, XP008071792, ISSN: 1742-5247, DOI: 10.1517/17425247.2.3.489 chapter 6</td>
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