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(54) Title: NOVEL PROCESS

(57) Abstract: The present invention provides a process for the production of an oil in water emulsion comprising the step of a) introducing an oil phase into a mixing device by applying a positive pressure in the oil phase containing tank.



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Novel process

Technical Field

5 The present invention relates to improved processes for the production of oil in water emulsions, in particular submicron oil in water emulsions comprising squalene.

Background to the invention

10 The present invention relates to processes for the production of oil in water emulsions. Methods of manufacture are disclosed in Ott *et al.*, 2000 (The Adjuvant MF59: A 10-year Perspective. Vaccine Adjuvants: Preparation methods and Research Protocols [Methods in Molecular medicine, Vol. 42, Chapter 12, p211-228], Ott *et al.*, 1995 (MF59 – Design and Evaluation of a Safe and Potent Adjuvant for Human Vaccines: Vaccine Design, the Subunit and Adjuvant Approach [Pharmaceutical Biotechnology volume 6] eds. Powell & Newman, WO06/100110A1 and Lidgate *et al.*, 1992 (Sterile Filtration of a Parenteral
15 Emulsion. Pharmaceuticals Research 9(7): 860-863).

Oil in water emulsions are often used in vaccine/immunogenic compositions as adjuvants. As these emulsions are administered to humans it is necessary that the emulsions are sterile. Oil in water emulsions used as adjuvants are submicron emulsions and the oil
20 droplets are sufficiently small to be sterile-filtered through 0.2µm filters. It is an object of the present invention to provide a process for the production of oil in water emulsions.

Summary of the Invention

25 The present invention relates to a process for production of submicron oil in water emulsion, in particular submicron oil in water emulsions comprising squalene. In particular, the present invention relates to a process for the production of an oil in water emulsion comprising the step of a) introducing an oil phase into a mixing device by applying a positive pressure in the oil phase containing tank.

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Brief description of Figures

35 **Figure 1:** Evolution of Z-average diameter of emulsion droplets with the number of passes and after filtration. Error bars are the standard deviations.

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Figure 2: Evolution of the polydispersity of emulsion droplets with the number of passes and after filtration. Error bars are the standard deviations.

Figure 3: Filterability, expressed as the capacity of the filter, of the emulsions after 3 passes, measured either on a 150 cm² membrane or on a 1300 cm² membrane. Error bars are the standard deviations.

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Detailed Description of the Invention

Oil in water emulsions are made by combining and mixing an oil phase (comprising one or more oils and optionally one or more surfactants) with an aqueous phase comprising a surfactant. The surfactant and microfluidisation allows a stable emulsion to be formed *i.e.* an emulsion that will not separate into oil and aqueous phases for at least 3 years.

10

The present inventors have demonstrated that by introducing an oil phase into a mixing device by applying positive pressure in a receptacle (for example a feeding tank) comprising the oil phase produces an oil in water emulsion with a reduced polydispersity, reduced droplet size and improved filterability compared to an oil in water emulsion in which the oil phase is introduced by, for example, a membrane pump.

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Accordingly, the present invention provides a process for the production of an oil in water emulsion comprising the step of a) introducing an oil phase into a mixing device by applying a positive pressure in the oil phase containing tank.

20

The pressure at which the oil and/or aqueous phases may be introduced can be readily determined by the person skilled in the art. In particular a embodiment, processes of the invention, the oil and/or aqueous phases are introduced into the mixing device by adjusting the pressure to about 2 to 6 bars, for example about 4 bar to about 5 bar, for example 4.5 bar.

25

In order for any oil in water composition to be suitable for human administration, the oil phase must comprise a metabolisable oil (*i.e.* biodegradable). The oil may be any vegetable oil, fish oil, animal oil or synthetic oil, which is not toxic to the recipient and is capable of being transformed by metabolism. Nuts, seeds, and grains are common sources of vegetable oils. Synthetic oils are also suitable. Accordingly, oil in water emulsions of the invention comprises a metabolisable oil, in a particular embodiment oil in water emulsions of the invention comprise squalene (for example between about 4% and 6% [v/v]).

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The oil phase may comprise one or more metabolisable oils. In a particular embodiment, the oil phase comprises squalene or squalane, in particular squalene. In a further embodiment of the invention the oil phase comprises a tocol and in a particular

embodiment of the invention the oil phase comprises α -tocopherol. In a further embodiment of the invention the oil phase comprises squalene and α -tocopherol.

5 The oil phase may further comprise a surfactant. Suitable surfactants are well known to the skilled person and include, but are not limited to polyoxyethylene sorbitan monooleate (TWEEN 80, POLYSORBATE 80), sorbitan triolate (SPAN 85), phosphatidylcholine (lecithin), polyoxyethylene (12) cetostearyl ether and octoxynol-9 (TRITON X-100). In a particular embodiment the oil phase comprises sorbitan triolate (SPAN 85). In a particular
10 embodiment of the invention the oil phase comprises squalene and sorbitan triolate (SPAN 85)

In a further embodiment of the invention there is provided a process as described herein further comprising the step b) introducing an aqueous phase into said mixing device by applying a positive pressure in the aqueous phase containing tank.

15 The aqueous phase used in the processes of the invention may be water, for example water for injection (WFI). However, it is preferable that the aqueous phases of the invention comprise a buffer. Suitable buffers are well known to the person skilled in the art and include but are not limited to a phosphate buffer, citrate buffer, Tris buffer, succinate buffer, maleate buffer or borate buffer. In a particular embodiment, the buffer is
20 selected from the group, phosphate buffered saline (PBS), modified PBS (PBS-mod) and citrate buffer. In a particular embodiment, the aqueous phase comprises a buffer, that when mixed with the oil phase will provide a substantially isotonic oil in water emulsion.

25 In a particular embodiment of the invention, the aqueous phase comprises one or more surfactants as described herein. In a particular embodiment of the invention, the aqueous phase comprises the surfactant polyoxyethylene sorbitan monooleate (TWEEN 80, POLYSORBATE 80).

30 In a particular embodiment of the invention the introduction of the aqueous phase [step b)] and the oil phase [step a)] are performed substantially simultaneously.

In a further embodiment of the invention the aqueous and oil phases as described herein are introduced at a ratio of about 90:10 or about 95:5 or about 97.5:2.5 or about
35 98.75:1.25 (percent v/v).

The term "mixing device" as used herein means a device suitable for mixing an oil phase and an aqueous phase to form an emulsion. In a particular embodiment of the invention the mixing device is a high shear mixing device. Suitable high shear mixing devices are
40 known to the skilled person and include, but are not limited to a high-speed blade homogeniser, an inline homogeniser, a colloid mill or a sonolator. In a particular embodiment of the invention the mixing device is a high-pressure homogeniser. Suitable

high pressure homogenizers are known to the skilled person and include, but are not limited to a fixed geometry microfluidiser or to a variable geometry high pressure homogenizer.

- 5 In a further embodiment of the invention there is provided a process as described herein further comprising the step c) mixing the oil and aqueous phases to form an oil in water emulsion.

10 Following mixing in step c) the oil in water emulsion may be a coarse oil in water emulsion if mixed in a high shear mixing device for example. In order to reduce the size of the oil droplets in the oil in water emulsion so that it is suitable for sterile filtration for example, the emulsion from step c) can be further processed in for example a high-pressure homogeniser.

- 15 Accordingly, in a further embodiment of the invention there is provided a process as described herein further comprising the step d) subjecting the oil in water emulsion of step c) to high pressure homogenization to form a submicron oil in water emulsion.

20 The skilled person can achieve the desired oil droplet size by varying the number of times the emulsion is passed through the high pressure homogeniser, as the oil droplet size will reduce after each cycle. Accordingly, in a one embodiment of the invention there is provided a process as described herein where in the emulsion is subjected to high pressure homogenisation [step f)] 1, 2, 3, 4, 5, 6, 7, 8 or more times.

- 25 In a further embodiment of the invention the high pressure homogenization is performed at a pressure of between about 10000 and about 20000, about 12000 and about 18000, about 14000 and about 16000 or about 15000 ± 1000 psi.

30 During high pressure homogenisation the temperature of the oil in water emulsion typically increases and thus in a one embodiment of the invention the oil in water emulsion is cooled to between about 15°C and about 30°C, about 16°C and about 29°C, about 17°C and about 28°C, about 16°C and about 27°C or between about 16 °C and about 28°C after the one or more, but at least the final time the emulsion is subjected to high pressure homogenisation.

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In a further embodiment, the processes of the invention comprise the steps:

- e. pre-filtering the oil in water emulsion; and
- f. filtering an oil in water emulsion filtered according to step e) through a sterile grade filter

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By "sterile grade filter" it is meant a filter that produces a sterile effluent after being challenged by microorganisms at a challenge level of greater than or equal to $1 \times 10^7/\text{cm}^2$

of effective filtration area. Sterile grade filters are well known to the person skilled in the art of the invention and have a pore size of about 0.2 μ m, and thus include filters with a pore size of about 0.22 μ m.

- 5 The filter used in the pre-filter (*i.e.* the filter used in step e) can have pores with the size ranging those of a sterile grade filter (*i.e.* about 0.2 μ m), to a pore size of about 2 μ m. In a particular embodiment the pore size of the pre-filter ranges from the size of those of a sterile grade filter sterile grade filter to the size of about 1 μ m. For example, the pore size of the filter used in step e) is about 2 μ m, about 2.5 μ m, about 1 μ m, about 0.9 μ m, about 10 0.8 μ m, about 0.9 μ m, about 0.7 μ m, about 0.6 μ m, about 0.5 μ m, 0.45 μ m or sterile grade for example about 0.2 μ m, for example 0.22 μ m.

- The membranes of the filter can be made from any suitable material known to the skilled person, for example, but not limited to cellulose acetate, polyethersulfone (PES), 15 polyvinylidene fluoride (PVDF), polytetrafluoroethylene (PTFE). In a particular embodiment of the invention one or more or all of the filter membranes of the present invention comprise polyethersulfone, for example hydrophilic polyethersulfone.

- In an embodiment of the invention, the submicron oil in water emulsions comprise 20 between about 2% and about 15%, about 4% and about 12% oil, about 5% and about 10%, about 4% and about 6%, about 8% and about 12%, for example about 5% or 10% (v/v) oil.

- The processes of the invention produce oil in water emulsions in which the oil droplets are 25 smaller, the polydispersity is reduced and/or the oil in water emulsion is more easily filtered compared to oil in water emulsions produced wherein the oil phase is introduced by means such as a membrane pump.

- Accordingly, the present invention provides an oil in water emulsion produced by the 30 processes as described herein.

- The oil in water emulsions of the present invention may be useful as adjuvants and may be combined with more or more antigens to produce immunogenic compositions. Accordingly, the present invention provides an immunogenic composition comprising oil in 35 water emulsions produced by the processes as described herein and an antigen.

In a further embodiment of the invention, there is provided a kit comprising: i) an oil in water emulsion produced by the processes as described herein; and (ii) an antigen.

- 40 Suitable antigens for use in immunogenic compositions or kits of the invention include but are not limited to antigens derived from influenza virus. In a particular, the influenza

antigen is subunit or a split influenza virus. The influenza antigen is either egg-derived or in particular cell culture derived.

Oil in water emulsions of the invention may also comprise a tocol. Tocols are well known in the art and are described in EP0382271. In particular, the tocol is α -tocopherol or a derivative thereof such as alpha-tocopherol succinate (also known as vitamin E succinate).

In a particular embodiment of the invention, there is provided an oil in water emulsion of the invention comprising squalene (for example about 5% [v/v]) and α -tocopherol (for example about 5% [v/v]).

Oil in water emulsions of the invention comprise one or more surfactants. Suitable surfactants are well known to the skilled person and include, but are not limited to polyoxyethylene sorbitan monooleate (TWEEN 80, POLYSORBATE 80), sorbitan trioleate (SPAN 85), phosphatidylcholine (lecithin), polyoxyethylene (12) cetostearyl ether and octoxynol-9 (TRITON X-100). In a particular embodiment of the invention oil in water emulsions comprise polyoxyethylene sorbitan monooleate (TWEEN 80, POLYSORBATE 80). In a further embodiment, oil in water emulsions of the invention comprise polyoxyethylene sorbitan monooleate (TWEEN 80, POLYSORBATE 80) and a further surfactant, in particular sorbitan trioleate (SPAN 85).

In a particular embodiment of the invention the oil in water emulsion comprises a metabolisable oil (e.g. squalene), a tocol (e.g. α -tocopherol) and a surfactant (e.g. polyoxyethylene sorbitan monooleate [TWEEN 80, POLYSORBATE 80]).

In a further embodiment of the invention, oil in water emulsions of the invention comprise a metabolisable oil (e.g. squalene), a surfactant (e.g. polyoxyethylene sorbitan monooleate [TWEEN 80, POLYSORBATE 80]), and optionally a second surfactant (e.g. sorbitan trioleate [SPAN 85]).

In a further embodiment of the invention, oil in water emulsions of the invention comprise a metabolisable oil (e.g. squalene), a polyoxyethylene alkyl ether hydrophilic non-ionic surfactant (e.g. polyoxyethylene (12) cetostearyl ether) and a hydrophobic non-ionic surfactant (e.g. polyoxyethylene sorbitan monooleate [(TWEEN 80, POLYSORBATE 80)]), or sorbitan trioleate [SPAN 85]).

The oil in water emulsions and immunogenic compositions as described herein are suitable for use in medicine and specifically for the prevention and/or treatment of disease.

Accordingly, there is provided an oil in water emulsion produced by the any processes described herein or an immunogenic composition as described herein for use in medicine.

5 In a further embodiment, there is provided an oil in water emulsion produced by the any processes described herein or the immunogenic composition as described herein for use in the prevention and/or treatment of disease in a mammal, in particular a human.

10 In a further embodiment, there is provided the use of an oil in water emulsion produced by the any processes described herein or the immunogenic composition as described herein in the manufacture of a medicament the prevention and/or treatment of disease in a mammal, in particular a human.

15 In a further embodiment, there is provided a method of treatment comprising the step of administering the oil in water emulsion produced by the any processes described herein or an immunogenic composition as described herein to a mammal, in particular a human.

Embodiments herein relating to "vaccine compositions" of the invention are also applicable to embodiments relating to "immunogenic compositions" of the invention, and *vice versa*.

20 The terms "comprising", "comprise" and "comprises" herein are intended by the inventors to be optionally substitutable with the terms "consisting of", "consist of" and "consists of", respectively, in every instance.

25 The term "about" in relation to a numerical value x means $x \pm 5\%$ or 10% .

Example

Method

Aqueous phase was prepared in tank 2, by mixing water for injection, phosphate buffer saline and Tween. Oily phase was prepared in tank 1, by mixing tocopherol and squalene.
30 Both phases were stirred until homogeneity was obtained. The whole installation was flushed with nitrogen in order to avoid tocopherol oxidation.

High pressure homogenizer was fed with a membrane pump. Both phases were fed together, with the required flow rate ratio. Both phases were first passed through a high shear homogenizer where a coarse emulsion was obtained. Then, in line with the high
35 shear homogenizer, the product entered the high pressure homogenizer, where the fine emulsion was obtained.

At the outlet of the mixing device, the product was harvested in tank 3 (first pass). When tank 2 and 1 were empty, emulsion from tank 3 was directed towards the inlet of the mixing device and a second pass was performed. At the end of the second pass, the product is harvested in tank 2. When tank 3 was empty, the emulsion from tank 2 was directed towards the inlet of the mixing device and a third pass was performed. The emulsion was harvested in tank 3 and stored under nitrogen until filtration.

In order to assess the influence of the feeding method, processes were also performed with the whole installation submitted to a positive feeding pressure. In order to reach this, tanks were pressurized with nitrogen or air.

10 Results

Size was measured by dynamic light scattering, a method based on light diffusion. Z-average diameter was smaller for processes using a membranes pump for the feeding compared to processes where the whole installation is submitted to positive pressure. This difference was larger at the beginning of the process (pass 1) but tended to vanish at the end of the process (filtrated product). Additionally, when feeding was performed with the whole system under positive pressure, the variability on size also decreased when passes were added. This is not the case when a membrane pump is used. See Figure 1.

Polydispersity was in the same range, whatever the feeding method but, the reproducibility was much better when the process is performed with the whole installation submitted to a positive pressure. See Figure 2.

Filterability was increased, and most importantly the reproducibility was improved, when the process is performed with the whole installation submitted to a positive pressure compared to a process for which the feeding is done with a membrane pump. See Figure 3.

25 Conclusion

Feeding the mixing device by submitting the whole installation to a positive pressure allows obtaining smaller droplet size and improved filterability. Moreover, it also improves the reproducibility of the process since standard deviation obtained on ZAD, PDI and filterability are smaller compared to a process for which the feeding is performed with a membrane pump.

CLAIMS

1. A process for the production of an oil in water emulsion comprising the step of a) introducing an oil phase into a mixing device by applying a positive pressure in the oil phase containing tank.
2. The process of claim 1 comprising the step b) introducing an aqueous phase into said mixing device by applying a positive pressure in the aqueous phase containing tank.
3. The process according to claim 1 or 2 wherein the oil and/or aqueous phases are introduced into the mixing device by adjusting the pressure to about 2 to 6 bars, for example about 4 bar to about 5 bar, for example 4.5 bar.
4. The process according to claim 2 or 3 wherein steps a) and b) are performed substantially simultaneously.
5. The process of any preceding claim wherein the aqueous and oil phases are introduced at a ratio of about 90:10, 95:5 or 98.75:1.25 (percent v/v).
6. The process of any preceding claim wherein the mixing device is a high shear homogenizer or a high pressure homogeniser.
7. The process of any one of claims 2 to 6 comprising the step c) mixing the oil and aqueous phases to form an oil in water emulsion.
8. The process of claim 7 further comprising the step of d) subjecting the oil in water emulsion of step c) to high pressure homogenization to form a submicron oil in water emulsion.
9. The process of claim 8 wherein step d) is performed 2, 3, 4, 5, or 6 times.
10. The process of claim 8 or 9 wherein the high pressure homogenization is performed at between about 10000psi and about 20000psi, about 12000psi and about 18000psi, about 14000psi and about 16000psi or about 15000±1000 psi.
11. The process of any one of claims 8 to 10 wherein oil in water submicron emulsion is cooled to between 15°C and 30°C, 16°C and 29°C, 17°C and 28°C, 16°C and 27°C or between 16 °C and 28°C following each time step d) is performed.

12. The process of any one of claims 8 to 11 further comprising the steps: comprising the steps:
- e. pre-filtering the oil in water emulsion; and
 - f. filtering an oil in water emulsion filtered according to step b) through a sterile grade filter.
13. The process of preceding claim wherein the oil in water emulsion comprises between 2% and 8% (v/v) oil.
14. The process of claim wherein the submicron oil in water emulsion comprises between 4% and 6% (v/v) oil.
15. The process of any preceding claim wherein the oil in water emulsion comprises between 8 and 12% (v/v) oil.
16. The process of any preceding claim wherein the oil phase comprises squalene.
17. The process of any preceding claim wherein the oil phase comprises a surfactant.
18. The process of claim 17 wherein the surfactant is sorbitan trioleate (SPAN 85).
19. The process of any preceding claim wherein the oil phase comprises a tocol.
20. The process of claim 19 wherein the tocol is α -tocopherol.
21. The process of any one of claims 2 to 20 wherein the aqueous phase comprises an aqueous solution and a surfactant.
22. The process of claim 21 wherein the surfactant is polyoxyethylene sorbitan monooleate (TWEEN 80, POLYSORBATE 80).
23. An oil in water emulsion produced by the process of any one of claims 1 to 22.
24. An immunogenic composition comprising an oil in water emulsion according to claim 23 and an antigen.
25. The oil in water emulsion of claim 23 or the immunogenic composition of claim 24 for use in medicine.
26. The oil in water emulsion of claim 23 or the immunogenic composition of claim 24 for use in the prevention and/or treatment of disease.

27. Use of the oil in water emulsion of claim 23 or the immunogenic composition of claim 24 in the manufacture of a medicament the prevention and/or treatment of disease.

5 28. A method of treatment comprising the step of administering the oil in water emulsion of claim 23 or an immunogenic composition of claim 24 to a mammal, for example a human.

10 29. A kit comprising i) the oil in water emulsion of claim 23; and (ii) an antigen.

30. An immunogenic composition of claim 23 or a kit of claim 29 wherein the antigen is derived from influenza virus.

Figures

Figure 1: Evolution of Z-average diameter of emulsion droplets with the number of passes and after filtration. Error bars are the standard deviations.

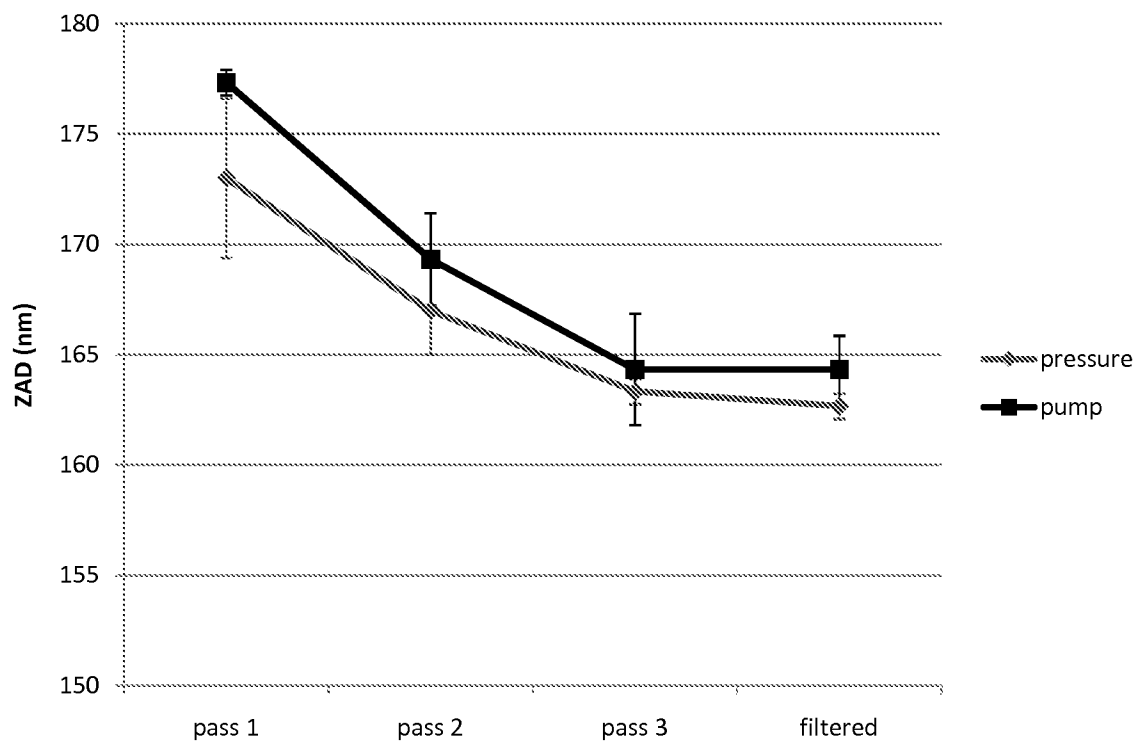


Figure 2: Evolution of the polydispersity of emulsion droplets with the number of passes and after filtration. Error bars are the standard deviations.

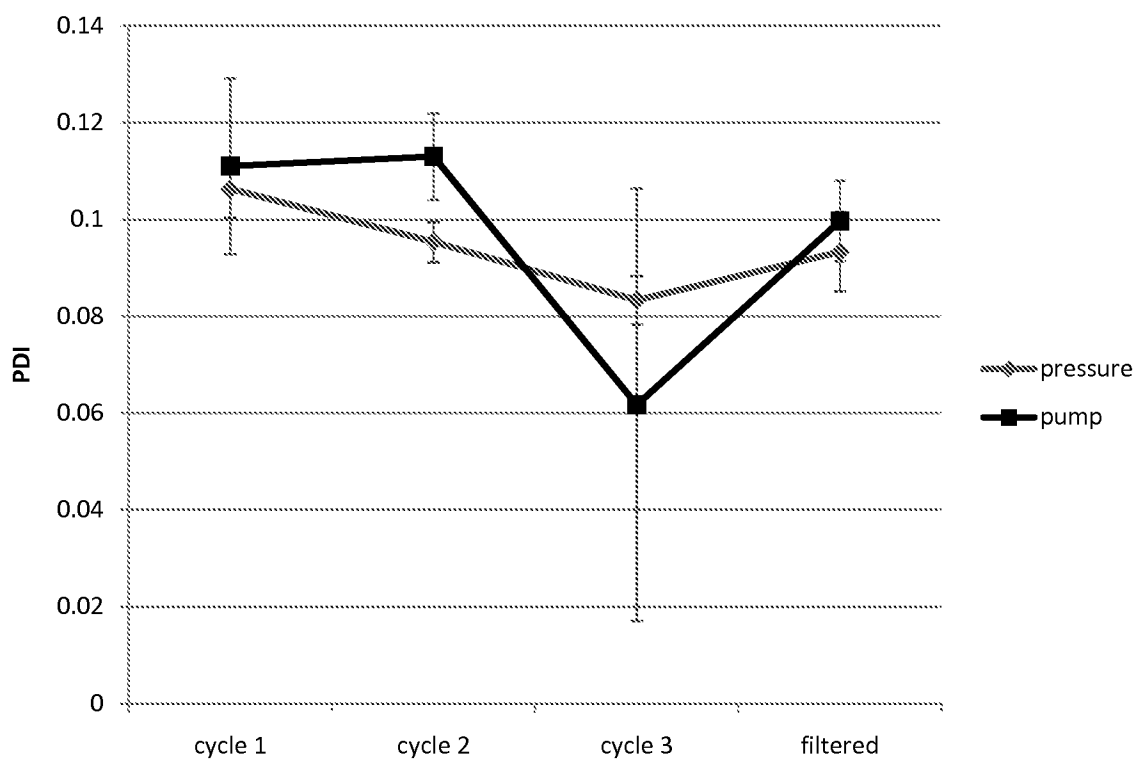
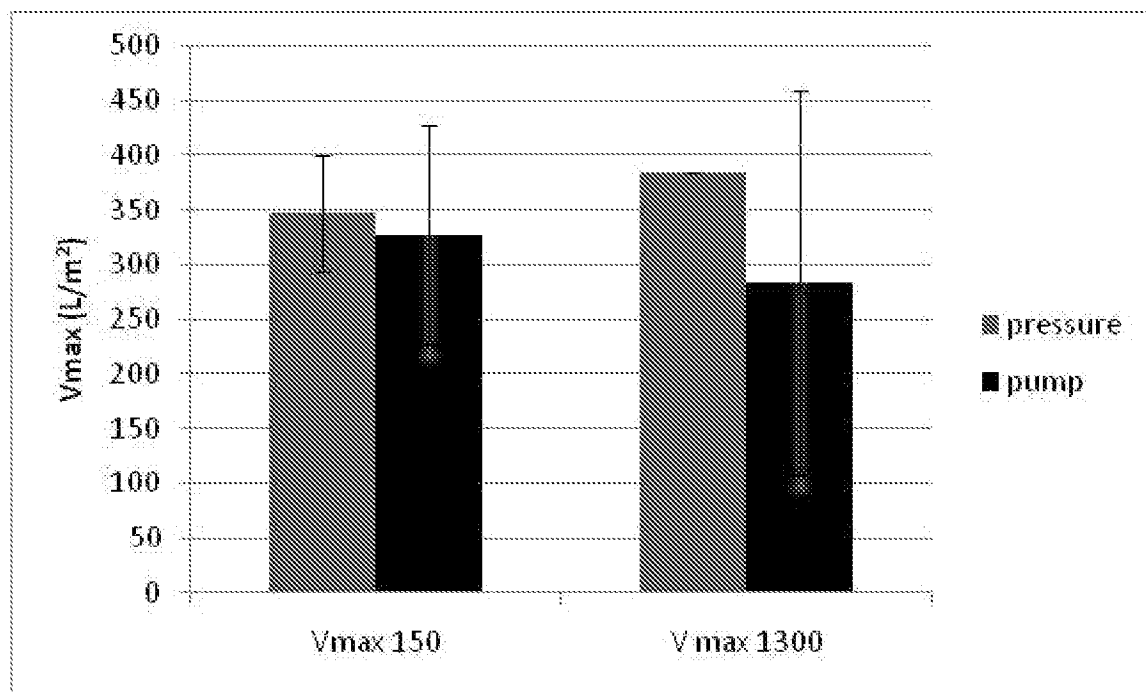


Figure 3: Filterability, expressed as the capacity of the filter, of the emulsions after 3 passes, measured either on a 150 cm² membrane or on a 1300 cm² membrane. Error bars are the standard deviations.



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/059488

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/107 A61K9/00 A61K39/00
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)
A61K

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

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

EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/087204 A2 (PFIZER PROD INC [US]; DOMINOWSKI PAUL JOSEPH [US]; KLOSE PAMELA KAY [U] 14 October 2004 (2004-10-14)	23-30
Y	claims 1-15 examples	1-30
X	WO 95/11700 A1 (PHARMOS CORP [US]; US ARMY [US]; LOWELL GEORGE H [US]; AMSELEM SHIMON) 4 May 1995 (1995-05-04)	23-29
Y	examples	1-30
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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"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

4 October 2011

Date of mailing of the international search report

14/10/2011

Name and mailing address of the ISA/

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Schüle, Stefanie

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/059488

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	I. BURGAUD ET AL: "An improved high-pressure homogenizer for making fine emulsions on a small scale", INTERNATIONAL JOURNAL OF FOOD SCIENCE AND TECHNOLOGY, vol. 25, no. 1, 1 February 1990 (1990-02-01), pages 39-46, XP55008283, ISSN: 0950-5423, DOI: 10.1111/j.1365-2621.1990.tb01057.x	1,2,4-7, 15,17,23
Y	page 40, paragraph 3 Technical description of jet homogenizer; page 40 - page 42	1-30
X	----- PERRIER-CORNET J M ET AL: "Comparison of emulsification efficiency of protein-stabilized oil-in-water emulsions using jet, high pressure and colloid mill homogenization", JOURNAL OF FOOD ENGINEERING, BARKING, ESSEX, GB, vol. 66, no. 2, 1 January 2005 (2005-01-01), pages 211-217, XP004565551, ISSN: 0260-8774, DOI: 10.1016/J.JFOODENG.2004.03.008	1,6,17, 23
Y	Materials and Methods; page 212 - page 213	1-30
Y	----- WO 2007/062831 A1 (GLAXOSMITHKLINE BIOLOG SA [BE]; GARCON NATHALIE MARIE-JOSEPHE [BE]; HA) 7 June 2007 (2007-06-07) examples -----	1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/059488

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004087204	A2	14-10-2004	AR 043803 A1 10-08-2005
		AU 2004226591 A1 14-10-2004	
		BR PI0408635 A 28-03-2006	
		CA 2521051 A1 14-10-2004	
		CL 6912004 A1 06-05-2005	
		CN 1767854 A 03-05-2006	
		EP 1613346 A2 11-01-2006	
		JP 2006522090 A 28-09-2006	
		KR 20060006909 A 20-01-2006	
		MX PA05010697 A 12-12-2005	
		NZ 542576 A 28-11-2008	
		RU 2009113834 A 20-10-2010	
		UY 28256 A1 30-11-2004	
		ZA 200507994 A 28-03-2007	
WO 9511700	A1	04-05-1995	AU 5543294 A 22-05-1995
WO 2007062831	A1	07-06-2007	CA 2630429 A1 07-06-2007
		EP 1951295 A1 06-08-2008	
		JP 2009517421 A 30-04-2009	
		US 2010266672 A1 21-10-2010	