



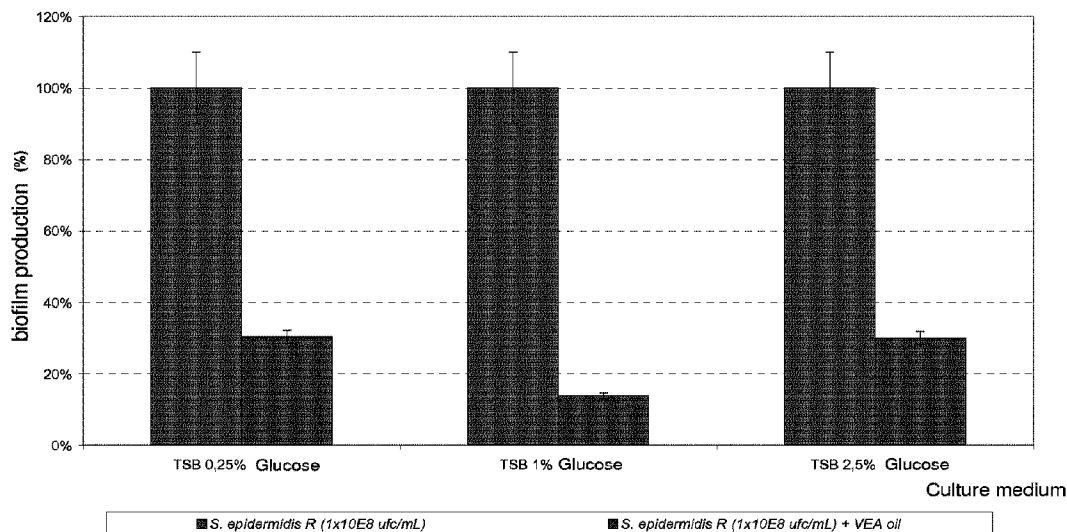
(86) **Date de dépôt PCT/PCT Filing Date:** 2018/05/28
(87) **Date publication PCT/PCT Publication Date:** 2018/12/06
(45) **Date de délivrance/Issue Date:** 2024/02/13
(85) **Entrée phase nationale/National Entry:** 2019/10/25
(86) **N° demande PCT/PCT Application No.:** EP 2018/063926
(87) **N° publication PCT/PCT Publication No.:** 2018/219862
(30) **Priorité/Priority:** 2017/05/29 (IT102017000058311)

(51) **Cl.Int./Int.Cl.** **A61K 31/355** (2006.01),
A61K 47/14 (2017.01), **A61K 47/24** (2006.01),
A61P 31/04 (2006.01), **A61P 31/10** (2006.01)
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(54) **Titre : FORMULATION A BASE DE VITAMINE E OU D'UN ESTER DE CELLE-CI POUR TRAITER LES BIOFILMS BACTERIENS ET FONGIQUES**

(54) **Title: FORMULATION BASED ON VITAMIN E OR AN ESTER THEREOF FOR TREATING BACTERIAL AND FUNGAL BIOFILMS**

Biofilm inhibition in the presence of VEA oil



(57) **Abrégé/Abstract:**

Formulation for topical use based on vitamin E or an ester thereof for use in removing, reducing or inhibiting a bacterial and/ or fungal biofilm, wherein said ester of vitamin E is an ester with a carboxylic acid of formula R-COOH, in which R is an alkyl radical having from 1 to 19 carbon atoms, or an alkenyl or alkynyl having from 2 to 19 carbon atoms.

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

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

06 December 2018 (06.12.2018)



(10) International Publication Number

WO 2018/219862 A1

(51) International Patent Classification:

A61K 31/355 (2006.01) A61P 31/04 (2006.01)

A61K 47/14 (2017.01) A61P 31/10 (2006.01)

A61K 47/24 (2006.01)

(21) International Application Number:

PCT/EP2018/063926

(22) International Filing Date:

28 May 2018 (28.05.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

102017000058311 29 May 2017 (29.05.2017) IT

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

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

(54) Title: FORMULATION BASED ON VITAMIN E OR AN ESTER THEREOF FOR TREATING BACTERIAL AND FUNGAL BIOFILMS

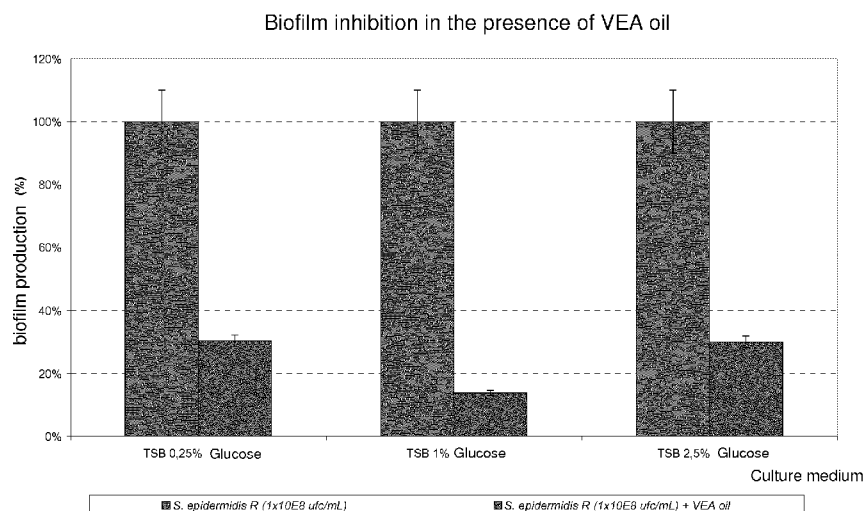


Figure 1

(57) Abstract: Formulation for topical use based on vitamin E or an ester thereof for use in removing, reducing or inhibiting a bacterial and/ or fungal biofilm, wherein said ester of vitamin E is an ester with a carboxylic acid of formula R-COOH, in which R is an alkyl radical having from 1 to 19 carbon atoms, or an alkenyl or alkynyl having from 2 to 19 carbon atoms.

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WO 2018/219862 A1

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

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Title: Formulation based on vitamin E or an ester thereof for treating bacterial and fungal biofilms

DESCRIPTION

Field of Application

- 5 The present invention refers to the technical field of the pharmaceutical industry.

In particular, the invention refers to a formulation for topical application for the treatment of a biofilm of pathogenic bacteria or fungi.

Prior art

- 10 It is known that a biofilm is a complex aggregation of microorganisms characterized by the secretion of an adhesive and protective extracellular matrix, defined EPS (extracellular polymeric substances).

- 15 Said matrix is not a static structure, since it is subjected to considerable variations depending on the type of microorganism that produces it and the growing conditions, although it is possible to identify the recurring presence of some polysaccharides, proteins and nucleic acids, and it represents a high percentage, varying from 50% to 90%, of the organic component of the biofilm, so much to be considered the primary element of this structure.

- 20 The biofilm can be present in any natural and artificial environment and is characterized by a noteworthy ability to adhere to surfaces, to guarantee complex interactions among the microbial communities contained therein and, further, to protect them from the action of external agents, including antibiotics.

- 25 Indeed, biofilm synthesis represents to date one of the most frequent complications of human infections, to the point of being object of numerous studies at international level.

The severity of such infections lies in the difficulty of diagnosis, in the difficulty of treating and eradicating the microbial community, as well as in the difficulty of prevention.

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Indeed, the resistance of this particular microbial community, often of the bacterial type, is considerable and the infections that result therefrom can sometimes cause death. It is estimated that about 65% of human infections are currently related to the production of this extracellular matrix, in which
5 the microorganisms reside and communicate with each other, being able to survive in even extreme environmental conditions.

The treatment of the biofilm-related infections is particularly difficult since the bacteria in this growth mode are intrinsically resistant to antimicrobial drugs and host defences.

10 A reduced diffusion of drugs through the extracellular matrix, the low growth rate of the cells, the increased ability to exchange genetic elements due to the proximity of the cells, the presence of subpopulations of dormant cells are all factors which are believed to contribute to the resistance of the biofilms to antibiotic treatment.

15 As a result, any biofilm prevention or disintegration strategy is useful to prevent infections, reducing hospitalizations and hospital costs.

Dhall S et al., (J Diabetes Res, 2014:562625) describe a treatment of injuries in a db/db mouse model having impaired healing by means of administration of alpha-tocopherol and N-acetyl cysteine. After the above-
20 mentioned treatment, it was noted that the biofilm had an increased sensitivity to antibiotics and granulation tissue was formed with proper collagen deposition and remodelling. However, alpha-tocopherol was administered intraperitoneally and only N-acetylcysteine was applied topically.

25 Lee AL et al., (Biomaterials, 2013 Dec; 34(38): 10278-86) describe biodegradable hydrogels based on polycarbonates functionalized with vitamin E moiety for antimicrobial application. These hydrogels showed antimicrobial/antifungal effects and the ability to reduce microbe viability of the biofilms.

30 Campoccia D et al., (J Biomed Res A, 2015 Apr; 103(4):1447-58) describe the possibility to use polylactic acid (PLA) polymers blended with vitamin E or vitamin E acetate as gentle anti-infective biomaterials. An *in vitro* experiment with biofilm-producing staphylococci proved a significant

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decrease in bacterial adhesion and in biofilm accumulation on the surface of these vitamin E (acetate)-enriched polymers.

Jagani S et al. (Biofouling, 2009; 25(4):321-4) evaluated, by microtiter-plate assay, the anti-biofouling activity of 14 phenols and natural phenolic compounds against *Pseudomonas aeruginosa* and it was shown that such
5 compounds, except ethyl linoleate and tocopherol, cause a significant reduction in biofilm formation by *Pseudomonas aeruginosa*.

The technical problem underlying the present invention was that of providing a formulation for topical application that is able to reduce or
10 remove pathogenic bacterial and/or fungal biofilms or to inhibit their formation, and that is suitable for application also on sensitive, intolerant or allergy-prone skin.

Summary of the Invention

The present invention solves the above-mentioned problem by providing a
15 formulation for topical use based on vitamin E or an ester thereof for use in removing, reducing or inhibiting a bacterial and/or fungal biofilm.

Preferably, the ester of vitamin E is an ester with a carboxylic acid of formula R-COOH, in which R is an alkyl radical having from 1 to 19 carbon atoms, or an alkenyl or alkynyl having from 2 to 19 carbon atoms.

20 Preferably, the ester is alpha-tocopheryl acetate, n-propionate or linoleate.

Preferably, the ester is alpha-tocopheryl acetate.

In an embodiment, the formulation according to the present invention consists of vitamin E or an ester thereof.

Preferably, the formulation consists of vitamin E acetate.

25 In another aspect, the formulation consists of alpha-tocopheryl acetate.

According to another embodiment, the formulation of the invention comprises, in weight percentage on the total weight of the formulation, 20 to 70% of vitamin E acetate and 20 to 70% of a volatile silicone.

The volatile silicone can be selected from the group comprising pentamer

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cyclomethicone, tetramer cyclomethicone, hexamer cyclomethicone, hexamethyldisiloxane, low viscosity dimethicone and mixtures thereof.

Preferably, the volatile silicone is a low viscosity dimethicone, such as for example one or more of the dimethicones Belsil DM2 and Belsil DM5 of the
5 firm Wacker or the dimethicones KF-96A-5cs and KF-96A-2cs of the firm Shin Etsu.

Preferably, the formulation further comprises 7 to 13% of hydrogenated castor oil.

Preferably, the formulation further comprises 7 to 15% of an oily component
10 chosen from the group comprising vegetable oils and esters of fatty acids such as octyl palmitate, isopropyl myristate, ethyl oleate and mixtures thereof.

Preferably, the formulation further comprises 2 to 3% of dimethiconol.

In a further embodiment, the formulation according to the present invention
15 comprises in weight percentage on the total weight of the formulation:

- from 20 to 65% of vitamin E acetate,
- from 20 to 60% of a vegetable butter or a wax,
- from 10 to 30% of a triglyceride of caprylic and capric acid,
- from 3 to 20% of a gelling agent for lipids selected from triglyceride of
20 palmitic and stearic acid and sorbitan olivate.

Preferably, the formulation further comprises one or more among hydrogenated castor oil, phytosterols, and ceramide.

Preferably, the vegetable butter is shea butter, and the ceramide is ceramide-NP.

25 By the expression "for topical use" it is hereby meant the use of the formulation by topical application onto a body part, in particular skin, mucosae, hair, nails.

The Applicant has surprisingly found that the formulation for topical

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application according to the present invention, based on vitamin E or an ester thereof, is able to effectively reduce formation of pathogenic bacterial and/or fungal biofilms, as shown in the Examples.

5 In an aspect of the present invention, the formulation according to the invention does not contain excipients nor additives and is therefore suitable for topical application also on sensitive, intolerant or allergy-prone skin.

The term "biofilm" identifies a community of microbial, bacterial or fungal nature, characterized by cells which adhere to a biotic or abiotic substrate immersed in a self-produced extracellular polymeric matrix which protects
10 them from the external environment.

Drawings

Figure 1 shows a bar graph of the biofilm production of the strain *Staphylococcus epidermidis* R on TSB medium with variable glucose concentration, with and without the formulation of Example 1 according to
15 the invention.

Figure 2 shows a bar graph of the biofilm production of the strain *Staphylococcus aureus* on TSB medium with variable glucose concentration, with and without the formulation of Example 1 according to the invention.

Detailed description

20 The present invention will be further described with reference to some non-limiting examples and referring also to the accompanying drawings.

EXAMPLE 1

An example of formulation that can be used for removing, reducing or inhibiting a bacterial and/or fungal biofilm is the product VEA® Olio,
25 marketed by the firm Hulka S.r.l. from Rovigo and consisting of alpha-tocopheryl acetate.

EXAMPLE 2

A formulation according to the invention in the form of a hydrophobic gel was prepared according to the following composition, wherein the
30 percentages are by weight on the total composition weight.

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	Pentamer cyclomethicone 245	39.5%
	Vitamin E acetate	30.0%
	Hydrogenated castor oil	10.5%
5	Octyl palmitate	10.0%
	8:2 Cyclomethicone / dimethiconol	10.0%

Such formulation was made according to the following procedure.

10 525 g of hydrogenated castor oil (Cutina HR) and 500 g of octyl palmitate were introduced into a steel-turbine mixer (manufactured by Dumec), and the content was stirred while being heated at about 80-90° temperature until the hydrogenated castor oil dissolved.

15 Then, 1500 g of vitamin E acetate were added under stirring at the above temperature, and the vacuum was produced inside the mixer (vacuum equal to 600 cmHg).

Once the desired degree of vacuum had been achieved, 500 g of a pre-formed mixture of 8:2 pentamer cyclomethicone/dimethiconol and 1975 g of pentamer cyclomethicone 245 were added under stirring.

20 The homogeneous mixture thus obtained was brought to ambient temperature under continuous stirring so as to obtain, in the end, a translucent hydrophobic gel of semisolid consistence.

25 100 small plastic jars containing 50 g each were filled with the gel prepared in this way and said jars were properly closed and subjected to a conservation test at different temperatures: - 20°C, 3°C and 30°C for 90 days, and 60°C for 21 days.

The aspect of the cream remained unchanged during the entire period of conservation at the above four temperatures, as well as its viscosity and the other rheological characteristics.

EXAMPLE 3

30 Another formulation according to the invention in the form of a hydrophobic gel was prepared according to the following composition, wherein the

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percentages are by weight on the total composition weight.

- tocopheryl acetate: 30%
- shea butter: 24%
- triglyceride of caprylic and capric acid: 21.7%
- 5 - sorbitan olivate: 14 %
- phytosterols: 10%
- ceramide-NP: 0.3%

10 The method of preparation is as follows: a first phase comprising Vitamin E, phytosterols and ceramides is prepared by heating the whole mixture up to 120 °C to obtain a homogeneous solution. The other ingredients are heated up to 60°C in a separate container. The two phases are then combined together and mixed for about 30 minutes at room temperature.

EXAMPLE 4

15 The selection of biofilm-producing strains for performing the *in vitro* tests described in the following Example 5 was carried out as follows.

At first, the selection envisaged a screening step on 30 strains of microorganisms, using a method to establish the production of biofilm by the assayed strains, which is described below.

20 The strains were cultured on TSB medium (tryptic soy broth, i.e. a nutritious medium which supports growth of a broad range of microorganisms) which was used for pre-inoculation.

25 Subsequently, the strains were subjected to the method for quantification of the produced biofilm according to Srdjan Stepanovic et al. (Stepanovic S., Vukovic D., Dakic I., Savic B., Svabic-Vlahovic M., "A modified microtiter-plate test for quantification of staphylococcal biofilm formation", Journal of Microbiological Methods 2000; 40:175-179) and said method is described below.

30 The tubes containing TSB previously incubated at 37°C for 24 hours were centrifuged at 3000 rpm for 10 minutes, the supernatant was then removed and the pellet was resuspended in the following media: TSB with 0.25%, 1% and 2.5% of D-glucose.

A 96-well plate containing 200 µl of bacterial suspension was then prepared

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and incubated at 37°C for 24 hours. Once the incubation period was ended, the content of the single wells was aspirated and the wells of the plate were washed 3 times with 250 µl of sterile physiological solution (NaCl 9 g/L) and, at each wash, the plate was turned upside down to remove excess physiological solution.

The cells were then fixed, adding to each well 200 µl of 99% methanol for 15 minutes; then, the wells were emptied and dried.

The 96-well plate was then stained for 5 minutes adding to each well 200 µl of a 2% crystal violet solution, after which the plate was washed with tap water and let to dry.

The dye bound to the adhering cells was re-solubilized with 160 µl of 33% glacial acetic acid (v/v) per well; the plate was read at the microplate reader (Victor) at a wavelength of 570 nm before and after adding the 33% glacial acetic acid.

For the purposes of comparative analysis of the results, a classification in four categories based on the adhesion ability of the tested strains, was introduced.

All strains were classified in the following categories: non adherent (0), weakly (+), moderately (++) or strongly (+++) adherent, depending on the optical density values of bacterial biofilms.

The limit ("*cut-off*") of the optical density (OD_c) for the microtiter-plate was defined as three standard deviations above the mean OD of the negative control.

The strains were classified as follows:

- $OD \leq OD_c$ - non adherent
- $OD_c < OD \leq 2 \times OD_c$ - weakly adherent
- $2 \times OD_c < OD \leq 4 \times OD_c$ - moderately adherent
- $4 \times OD_c < OD$ - strongly adherent

All the tests were performed in triplicates and the average of the results

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was calculated.

After such screening step was concluded, the microbial strains used for the *in vitro* tests were *Staphylococcus epidermidis* R (isolated from clinical samples) and *Staphylococcus aureus* (isolated from clinical samples).

5 **EXAMPLE 5**

The Applicant tested the ability to reduce, remove and inhibit biofilm of *Staphylococcus epidermidis* R and *Staphylococcus aureus* of the product VEA® Olio, marketed by the firm Hulka S.r.l., consisting of alpha-tocopheryl acetate 100%.

- 10 A 96-well plate was prepared in quadruplicate for each condition envisaged by the experiment, all the tests were performed on TSB with 0.25%, 1% and 2.5% of D-glucose.

The set out conditions were the following:

- 15 1. *Staphylococcus epidermidis* R and *Staphylococcus aureus* (with a count of 1×10^8 cfu/mL) without adding VEA Olio (positive control);
2. *Staphylococcus epidermidis* R and *Staphylococcus aureus* (with a count of 1×10^8 cfu/mL) loaded in the well only after uniformly coating the plate well with VEA Olio.

20 Figure 1 shows that, on TSB medium with 0.25% of glucose, biofilm production by the strain *Staphylococcus epidermidis* R was 30% with a 70% reduction of the production in the presence of VEA Olio.

In TSB medium with 1% of glucose, the above strain showed a biofilm production of 14% with a reduction of 86% in the presence of VEA Olio, while on TSB medium with 2.5% of glucose it showed a production of 30%
25 with a consequent reduction of 70% in the presence of VEA Olio.

Figure 2 shows that, on TSB medium with 0.25% of glucose, the biofilm production by the strain *Staphylococcus aureus* was 50%, with a 50% reduction of the production in the presence of VEA Olio.

In TSB medium with 1% of glucose, the strain at issue showed a biofilm
30 production of 32% with a reduction of 68% in the presence of VEA Olio,

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while on the TSB medium with 2.5% of glucose it showed a production of 50% with a consequent reduction of 50% in the presence of VEA Olio.

These results show that alpha-tocopheryl acetate used for the experiments plays a surprising inhibitory activity with respect to biofilm formation.

5 EXAMPLE 6

VEA® Olio was also tested for the ability to reduce, remove and inhibit biofilm of the following microorganisms: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Pseudomonas putida* (Table 1).

A 96-well plate was prepared in quadruplicate for each condition envisaged by the experiment, all the tests were performed on TSB with or without VEA® Olio.

Table 1: Biofilm production on TBS medium with or without VEA Olio.

	Medium	Mean OD*	Standard Deviation	Test T	D**	Biofilm production
S.aureus ATCC 29213	TSB	0,33	0,04	0,07	0,26	100%
	TSB +VEA Olio	0,26	0,05		0,11	44%
S.epidermidis [Code R9]	TSB	0,53	0,07	0,03	0,45	100%
	TSB + VEA Olio	0,33	0,13		0,18	39%
E.coli ATCC 11775	TSB	0,36	0,10	0,96	0,28	100%
	TSB +VEA Olio	0,35	0,15		0,20	73%
K.pneumonie ATCC 700603	TSB	0,41	0,10	0,87	0,34	100%
	TSB +VEA Olio	0,40	0,06		0,26	76%
P.mirabilis CECT 4168	TSB	0,36	0,07	0,16	0,28	100%
	TSB +VEA Olio	0,28	0,06		0,14	49%

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A.baumannni ATCC 19606	TSB	0,34	0,06	0,88	0,26	100%
	TSB +VEA Olio	0,34	0,07		0,20	76%
P.aeruginosa ATCC 27853	TSB	0,33	0,08	0,25	0,25	100%
	TSB +VEA Olio	0,27	0,05		0,12	49%
P.putida	TSB	0,45	0,09	0,03	0,38	100%
	TSB +VEA Olio	0,30	0,07		0,15	39%
No microorganism inoculated (blank)	TSB	0,08				
	TSB +VEA Olio	0,15				

*OD is the optical density at 570 nm.

**D is the difference between the mean optical density measured for each microorganism and the optical density of the blanks (TSB and TSB
5 VEA Olio respectively).

Table 1 shows that biofilm production by several types of microorganisms was strongly inhibited on medium TSB+VEA Olio.

For example, the biofilm production by *P. aeruginosa* was 49%, *S.epidermidis* was 39% and *S.aureus* was 44%, considering the biofilm
10 production on TSB medium as 100%.

These results show that alpha-tocopheryl acetate used for these experiments displays a surprising inhibitory activity with respect to biofilm formation by different microorganisms.

EXAMPLE 7

15 The gel obtained according to Example 2 was tested for the ability to reduce, remove and inhibit biofilm of same microorganisms cited in Example 6 (Table 2).

The experimental conditions were the same of Example 6.

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Table 2: Biofilm production on TBS medium with or without gel according to Example 2.

	Medium	Mean OD*	Standard Deviation	Test T	D**	Biofilm production
S.aureus ATCC 29213	TSB	0,35	0,11	0,0034	0,28	100%
	TSB+ GEL	0,69	0,10		0,17	62%
S.epidermidis [Code R9]	TSB	0,58	0,10	0,1335	0,51	100%
	TSB + GEL	0,69	0,08		0,16	33%
E.coli ATCC 11775	TSB	0,30	0,07	0,0035	0,23	100%
	TSB + GEL	0,64	0,13		0,12	53%
P.mirabilis CECT 4168	TSB	0,42	0,10	0,0058	0,34	100%
	TSB + GEL	0,66	0,07		0,14	41%
A.baumannni ATCC 19606	TSB	0,37	0,09	0,0021	0,30	100%
	TSB + GEL	0,68	0,08		0,16	53%
P.aeruginosa ATCC 27853	TSB	0,38	0,08	0,0273	0,31	100%
	TSB + GEL	0,69	0,20		0,17	54%
P.putida	TSB	0,35	0,08	0,0069	0,28	100%
	TSB + GEL	0,69	0,15		0,17	60%
No microorganism (blank)	TSB	0,07				
	TSB + GEL	0,52				

5 *OD is the optical density at 570 nm.

**D is the difference between the mean optical density measured for each microorganism and the optical density of the blanks (TSB and TSB + GEL respectively).

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Table 2 shows that biofilm production by several types of microorganism was strongly inhibited on medium TSB+GEL (according to Example 2).

For example, the biofilm production by *P. aeruginosa* was 54%, *P.mirabilis* was 41% and *S.epidermidis* was 33%, considering the biofilm production on

5 TSB medium as 100%.

Claims:

1. A formulation for topical use consisting of vitamin E or an ester thereof for a therapeutic use in removing, reducing or inhibiting a bacterial and/or fungal biofilm,

wherein said ester of vitamin E is an ester with a carboxylic acid of formula $R\text{-COOH}$, in which R is an alkyl radical having from 1 to 19 carbon atoms, or an alkenyl or alkynyl having from 2 to 19 carbon atoms.

2. The formulation for the use according to claim 1, wherein said ester is alpha-tocopheryl acetate, n-propionate or linoleate.

3. The formulation for the use according to claim 2, wherein said ester is alpha-tocopheryl acetate.

4. The formulation for the use according to claim 1, consisting of alpha-tocopheryl acetate.

5. A formulation for topical use comprising in weight percentages on the total weight of the formulation, 20 to 70% of vitamin E acetate and 20 to 70% of a volatile silicone for a therapeutic use in removing, reducing or inhibiting a bacterial and/or fungal biofilm.

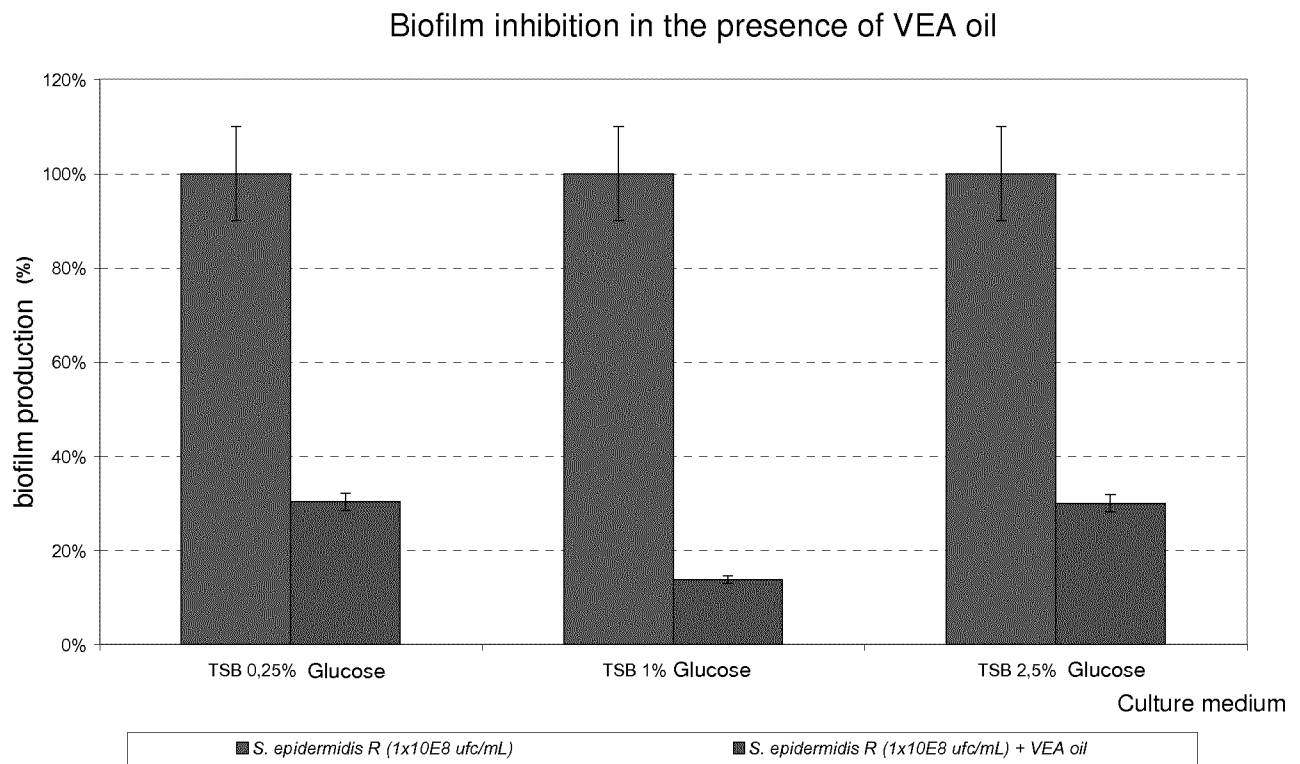
6. The formulation for the use according to claim 5, wherein said volatile silicone is selected from the group consisting of pentamer cyclomethicone, tetramer cyclomethicone, hexamer cyclomethicone, hexamethyldisiloxane, low viscosity dimethicone and mixtures thereof.

7. The formulation for the use according to claim 6, further comprising 7 to 13% of hydrogenated castor oil by weight of the total weight of the formulation.

8. The formulation for the use according to claim 7, further comprising 7 to 15% by weight of the total weight of the formulation of an oily component selected from the group consisting of vegetable oils and esters of fatty acids,

wherein the esters of fatty acids are selected from the group consisting of octyl palmitate, isopropyl myristate, ethyl oleate and mixtures thereof.

9. The formulation for the use according to claim 8, further comprising 2 to 3% of dimethiconol by weight of the total weight of the formulation.

**Figure 1**

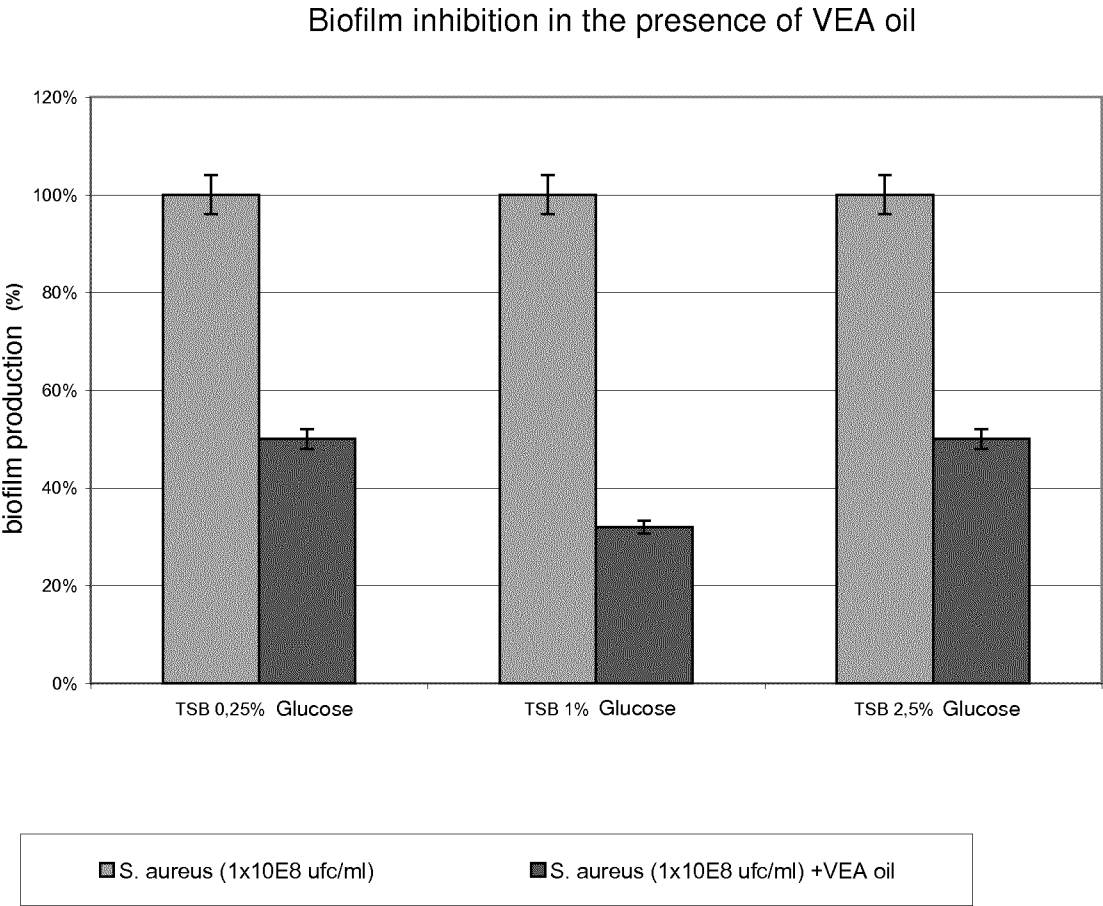


Figure 2

Biofilm inhibition in the presence of VEA oil

