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(54) Title: DEVICE FOR THE TOPICAL DELIVERY OF NITRIC OXIDE TO A SKIN SURFACE

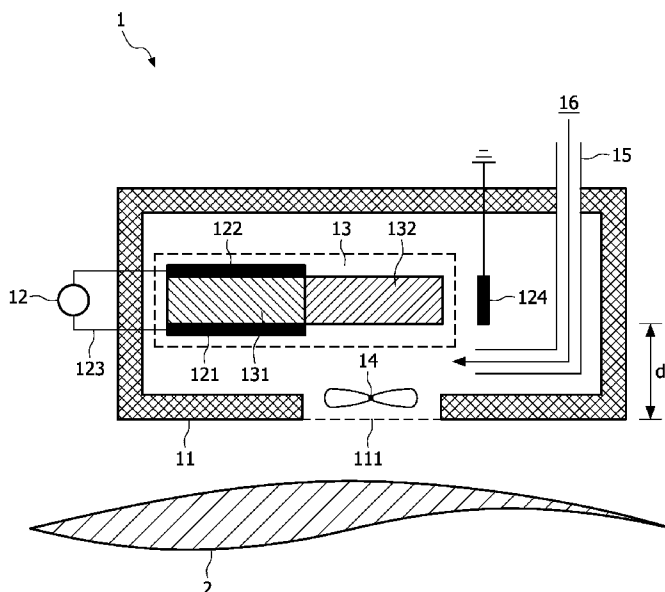


FIG. 1

(57) Abstract: The invention relates to a device (1) for the topical delivery of nitric oxide to a skin surface, the device comprising a piezoelectric transformer (13) as a means for generating the nitric oxide. The device according to the invention is suitable for use by a patient in a home environment.

WO 2009/093169 A1

Device for the topical delivery of nitric oxide to a skin surface

## FIELD OF THE INVENTION

The invention relates to a device for the topical delivery of nitric oxide to a skin surface.

## 5 BACKGROUND OF THE INVENTION

Skin disorders, such as tissue wounds, inflammatory or autoimmune skin diseases, are a rapidly increasing problem, presumably resulting as a consequence of environmental impacts on the human body. For example, 3 % of the global population suffers from neurodermatitis which is a chronic persistent allergic disease with 10 % of all children  
10 being affected. Another 3 % of the world population suffers from psoriasis. These numbers add up to about 400 million people, with an annual increase of 5 to 10 %.

Nowadays, many of these skin disorders are treated chemically, for example with corticosteroids (such as cortisone), topical steroid crèmes, ointments and moisturizers. Unfortunately, long term use of chemicals such as cortisone leads to severe side effects.  
15 Local treatments may result in additional skin allergies, skin thinning, teleangiectasy, striae and acne. In case of large area treatments, absorption in the blood stream may cause obesity, edema, growth delay, diabetes and hypertension. In addition, the risk of suffering from thrombosis and kidney disturbances may be increased. Therefore, there is an urgent need for a treatment of skin disorders that does not involve the use of the aforementioned chemicals.

20 Recently medical researchers have increasingly witnessed that nitric oxide has a positive influence on skin disorders. In a human body, nitric oxide is produced from oxygen molecules and  $\alpha$ -amino acids by the biosynthesis of enzymes. Nitric oxide is also synthesized in human skin. It is known that nitric oxide plays a central role in protecting the human body against invading pathogens and tumor cells, and in healing inflammatory cells  
25 and tissues.

Hence, many skin disorders may be healed and the healing process may be accelerated by introducing nitric oxide directly to the affected parts of skin cells and tissues from an external source. The mediating activities due to externally provided nitric oxide are identical or very similar to that of the nitric oxide synthesized in the human body, as long as

an appropriate amount of nitric oxide is dosed. No chemical substances other than those existing in the human body are involved. Consequently, side effects as described hereinbefore are not expected to occur. Since both the lifetime of nitric oxide in the atmosphere and that of nitric oxide dissolved in a bodily fluid are at most in the order of a millisecond, the activity of nitric oxide is well controlled by its dose amount and duration.

A device for forming a nitric oxide containing gas flow to treat a biological object is known from US20050218007A1. In the known device the nitric oxide containing gas flow is formed from a source gas comprising oxygen and nitrogen in a housing comprising two electrodes insulated from each other, a stationary arc discharge being generated and maintained between the electrodes. In other words, the known device comprises a relatively large discharge device, a gas cylinder and a power supply. The known device may be adequately applied for the treatment of a skin disorder in a professional environment with sufficient equipment and infrastructure, such as a hospital, but for many patients who suffer daily from a painful chronic skin disease it is a burden to visit such a place on a regular basis.

#### SUMMARY OF THE INVENTION

It is an object of the invention to provide a device for or the topical delivery of nitric oxide to a skin surface, that can be used easily and regularly by a patient in a home environment.

This object is realized with a device according to the opening paragraph, comprising a power supply and a piezoelectric transformer having a resonance frequency, the piezoelectric transformer comprising an input section and an output section, wherein the power supply is arranged to apply an alternating input voltage having an alternation frequency to the input section of the piezoelectric transformer in order to create an alternating output voltage at the output section, the alternation frequency being substantially equal to the resonance frequency.

When the input voltage has an alternation frequency that is substantially equal to the resonance frequency of the piezoelectric transformer, a high alternating output voltage is created at the output section of the piezoelectric transformer, enabling the generation of an electrical discharge in the ambient atmosphere. The electrical discharge produces nitrogen atoms and oxygen atoms due to the dissociation of nitrogen molecules and oxygen molecules present in the ambient air, respectively. The nitrogen and oxygen atoms recombine to form nitric oxide that subsequently diffuses towards the skin surface.

Piezoelectric transformers are known in the art as such, see for example J. Yang, *Analysis of Piezoelectric Devices*, World Scientific (2006). It is also known to use a piezoelectric transformer to generate an electrical discharge in an ambient atmosphere. For example, K. Teranishi *et al.*, *IEEE Transactions On Plasma Science*, Vol. 33, No. 2 (April 2005) discloses a piezoelectric transformer that is used to generate a dielectric barrier discharge in atmospheric pressure. However, it is not known in the art to use a piezoelectric transformer in a device for the topical delivery of nitric oxide to a skin surface.

An embodiment of the device according to the invention is defined in claim 2. In this embodiment, the piezoelectric transformer is positioned within a housing having an opening enabling a communication between the piezoelectric transformer and the skin surface via the ambient atmosphere, such that the shortest distance between the output section of the piezoelectric transformer and the opening of the housing is at least 1 micrometer per volt of the alternating output voltage. For example, when the output voltage at the output section of the piezoelectric transformer is 1 kV, the shortest distance between the output section and the opening of the housing is at least 1 millimeter. This embodiment is arranged to prevent the direct flow of an electrical current from the output side of the piezoelectric transformer to the skin surface. In many cases, such an electrical current may cause pain and destruction or irreparable damage of skin cells.

An embodiment of the device according to the invention is defined in claim 3. In this embodiment, the device further comprises a grounded electrode adjacent to the output section of the piezoelectric transformer. This embodiment is arranged to prevent the direct flow of an electrical current from the output side of the piezoelectric transformer to the skin surface.

An embodiment of the device according to the invention is defined in claim 4. In this embodiment, the device further comprises an air displacement device. This embodiment enables the diffusion process of nitric oxide to be controlled.

An embodiment of the device according to the invention is defined in claim 5. In this embodiment, the device further comprises a unit for providing a gas flow in the vicinity of the piezoelectric transformer and the skin surface. This embodiment enables a gas mixture that is desired for a particular electrical discharge to be supplied.

## BRIEF DESCRIPTION OF THE DRAWINGS

Examples of the invention will now be described in detail with reference to the accompanying drawings, in which:

Fig. 1 is a schematic cross section of the device according to the invention;

5 It should be noted that this figure is diagrammatic and not drawn to scale. For the sake of clarity and convenience, relative dimensions and proportions of parts of this figure have been shown exaggerated or reduced in size.

## DETAILED DESCRIPTION OF THE EMBODIMENTS

10 A cross section of a device 1 according to the invention is shown in Fig. 1. The device 1 comprises a housing 11, a power supply 12, and a piezoelectric transformer 13.

The housing 11 comprises an opening 111 enabling a communication between the piezoelectric transformer 13 and a skin surface 2 via the ambient atmosphere.

15 The piezoelectric transformer 13 has an input section 131 and an output section 132, the input section 131 being provided on two opposite sides with a first electrode 121 and a second electrode 122, respectively.

20 The power supply 12 is a standard AC power supply capable of supplying, across the first electrode 121 and the second electrode 122 of the input section 131 of the piezoelectric transformer 13, an alternating input voltage 123 having a magnitude in a range of approximately 10 V to 100 V, with an alternation frequency in a range of approximately 1 kHz to 500 kHz, and with an output power in a range of approximately 10 W to 100 W. The power supply 12 may either be present inside or outside the housing 11.

The first electrode 121 and the second electrode 122 are both copper electrodes, but the skilled person will understand that other suitable metallic electrodes exist.

25 The piezoelectric transformer 13 comprises a rectangular piece of single-layer piezoelectric material, such as barium titanate ( $\text{BaTiO}_2$ ), lead titanate ( $\text{PbTiO}_3$ ), lead zirconate ( $\text{PbZrO}_3$ ), or lead titanate zirconate ( $\text{PbZr}_x\text{Ti}_{1-x}\text{O}_3$ , wherein  $0 < x < 1$ ). Although piezoelectric transformers of any size and dimension can be used for the purpose of the invention, the piezoelectric transformer 13 has a length of 3.3 cm, a width of 2.3 cm, and a  
30 thickness of 0.8 mm. The piezoelectric transformer 13 has a resonance frequency of approximately 84 kHz in the longitudinal direction.

When the alternation frequency of the alternating input voltage 123 is substantially equal to the resonance frequency of the piezoelectric transformer 13, a high voltage step-up ratio is obtained. Under these resonance conditions, when the alternating

input voltage 123 has a magnitude of approximately 100 V, an alternating output voltage is obtained at the output section 132 of the piezoelectric transformer 13 that is sufficiently high to enable the creation of small contracted electrical discharges under atmospheric pressure on the surface of the output section 132 of the piezoelectric transformer 13. In the electrical discharges, nitric oxide is produced by the recombination of nitrogen atoms and oxygen atoms that have been created due to the dissociation of nitrogen molecules and oxygen molecules, respectively.

Since the lifetime of nitric oxide produced in air is expected to be in the order of a second at most, in order to provide nitric oxide at a concentration that is high enough to obtain the desired effect, the output section 132 of the piezoelectric transformer 13 is preferably positioned in the vicinity of the skin to be treated. When the distance between the output section 132 of the piezoelectric transformer 13 and the skin surface is more than 30 cm, the amount of nitric oxide that is created at the output section 132 and that is subsequently able to reach the skin surface is negligible.

However, a direct flow of electrical current from the output side 132 of the piezoelectric transformer 13 to the skin surface should preferably be prevented, as in many cases such a direct flow of electrical current may cause pain and destruction or irreparable damage of skin cells. Therefore, in the device 1, the piezoelectric transformer 13 is positioned within the housing 11 such that the shortest distance  $d$  between the output section 132 of the piezoelectric transformer 13 and the opening 111 of the housing 11 is at least 1 micrometer per volt of the alternating output voltage that is created at the output side 132 of the piezoelectric transformer 13. For example, when the device 1 is arranged to operate at an output voltage, at the output section 132 of the piezoelectric transformer 13, of 1 kV, the shortest distance  $d$  between the output section 132 and the opening of the housing 111 is at least 1 millimeter.

A further safety measure is present in the device 1, in the form of a grounded electrode 124 adjacent to the output section 132 of the piezoelectric transformer 13.

In order to better control the diffusion process of nitric oxide from the piezoelectric transformer 13 to the skin surface 2, the device 1 comprises a ventilator 14. The skilled person will understand that for this purpose other air displacement devices can also be used, such as a pump or a heating element that is arranged to displace air by means of a thermal chimney effect caused by local differences in air density.

The device 1 also comprises a unit 15 for providing a gas flow 16 in the vicinity of the output section 132 of the piezoelectric transformer 13, which is useful in case a certain gas mixture is desired for the electrical discharges.

5 As it is often the case that the area of the skin that is to be treated depends on the type and/or nature of the skin disorder, the device according to the invention may comprise a plurality of piezoelectric transformers 13, that can for instance be assembled as a matrix, which can be addressed by an external control circuit.

10 The device 1 can be used in a liquid or on a liquid surface. When the skin that is to be treated is wet, the part with the piezoelectric transformer 13 may be directly placed on the wet skin surface for the treatment.

While the invention has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive; the invention is not limited to the disclosed embodiments. Variations to the disclosed embodiments can be understood and effected by those skilled in 15 the art in practicing the claimed invention, from a study of the drawings, the disclosure, and the appended claims. In the claims, the word “comprising” does not exclude other elements, and the indefinite article “a” or “an” does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the 20 claims should not be construed as limiting the scope.

## CLAIMS:

1. A device (1) for the topical delivery of nitric oxide to a skin surface (2), the device (1) comprising a power supply (12) and a piezoelectric transformer (13) having a resonance frequency, the piezoelectric transformer (13) comprising an input section (131) and an output section (132), wherein the power supply (12) is arranged to apply an  
5 alternating input voltage (123) having an alternation frequency to the input section (131) of the piezoelectric transformer (13) in order to create an alternating output voltage at the output section (132), the alternation frequency being substantially equal to the resonance frequency.
2. The device (1) according to claim 1, wherein the piezoelectric transformer (13)  
10 is positioned within a housing (11) having an opening (111) enabling a communication between the piezoelectric transformer (13) and the skin surface (2) via the ambient atmosphere, such that the shortest distance ( $d$ ) between the output section (132) of the piezoelectric transformer (13) and the opening (111) of the housing (11) is at least 1 micrometer per volt of the alternating output voltage.  
15
3. The device (1) according to claim 1, further comprising a grounded electrode (124) adjacent to the output section (132) of the piezoelectric transformer (13).
4. The device (1) according to claim 1, further comprising an air displacement  
20 device (14).
5. The device (1) according to claim 1, further comprising a unit (15) for providing a gas flow (16) in the vicinity of the output section (132) of the piezoelectric transformer (13).



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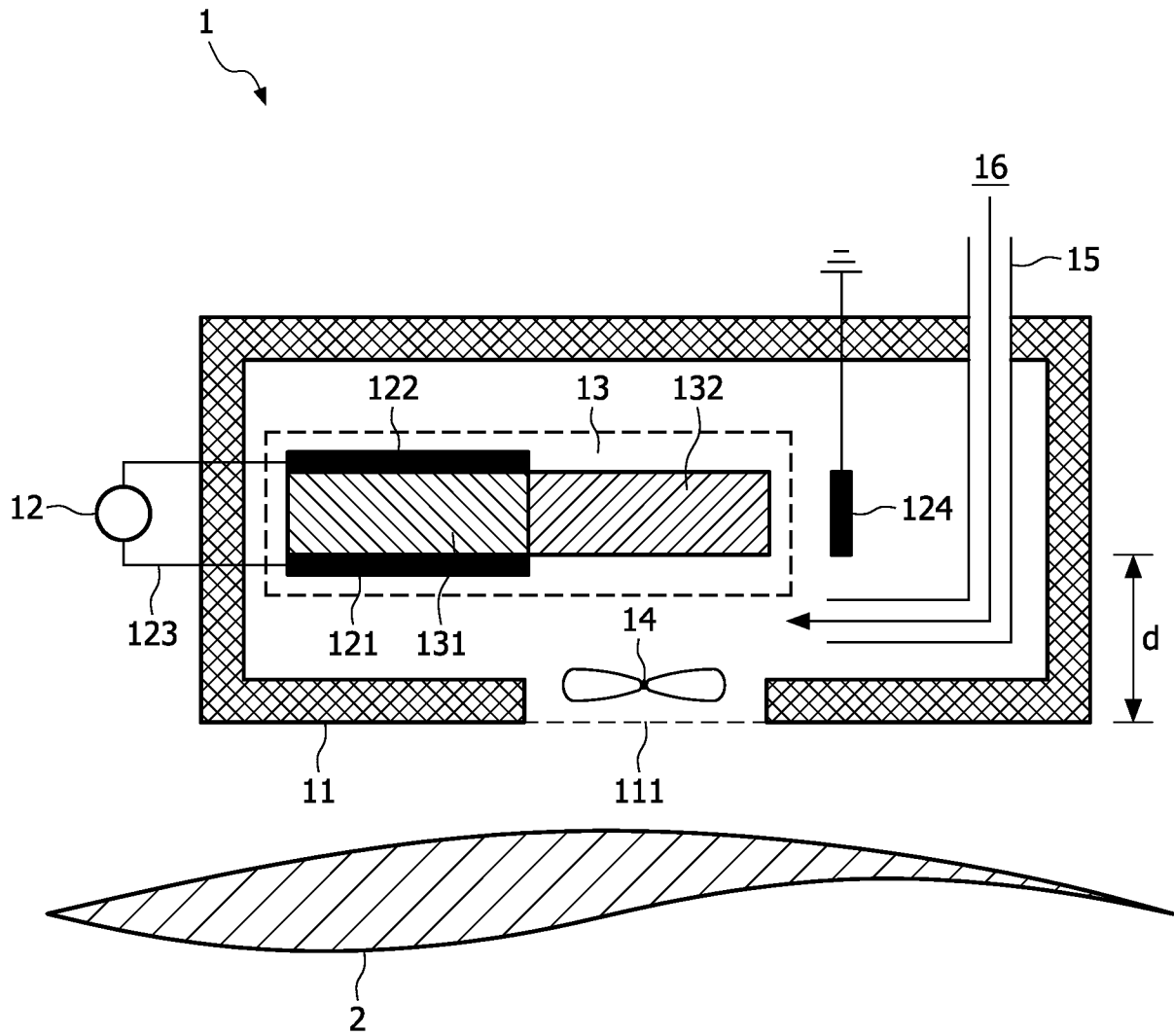


FIG. 1

# INTERNATIONAL SEARCH REPORT

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**A. CLASSIFICATION OF SUBJECT MATTER**  
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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)  
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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, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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A	WO 93/17741 A (GEN HOSPITAL CORP [US]) 16 September 1993 (1993-09-16) the whole document -----	1-5
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A	US 2007/190184 A1 (MONTGOMERY FREDERICK J [US] ET AL) 16 August 2007 (2007-08-16) the whole document -----	1-5
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Further documents are listed in the continuation of Box C.       See patent family annex.

\* Special categories of cited documents :

<p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p>	<p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*&amp;* document member of the same patent family</p>
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Date of the actual completion of the international search  <b>30 March 2009</b>	Date of mailing of the international search report  <b>08/04/2009</b>
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Name and mailing address of the ISA/ European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  <b>Rodrigues, Elodie</b>
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International application No  
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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