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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 September 2015 (03.09.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/130707 A3

(51) International Patent Classification:
*A61K 9/14* (2006.01)

(21) International Application Number:
PCT/US2015/017379

(22) International Filing Date:
24 February 2015 (24.02.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|---|---|---|
| 61/944,340 | 25 February 2014 (25.02.2014) | US |
| 62/027,139 | 21 July 2014 (21.07.2014) | US |
| 62/035,221 | 8 August 2014 (08.08.2014) | US |
| 62/067,350 | 22 October 2014 (22.10.2014) | US |


(71) Applicant: **OCULEVE, INC.** [US/US]; 395 Oyster Point Boulevard, Suite 501, South San Francisco, CA 94080 (US).

(72) Inventors: **LOUDIN, James, Donald**; 203 Kilts Drive, Houston, TX 77024 (US). **GUPTA, Amitava**; 5322 Fox Den Road, Roanoke, VA 24018 (US). **WARDLE, John**; 1802 Arriba Lane, San Clemente, CA 92672 (US). **STIVERS, Christopher, William**; 635 Tennessee Street, #401, San Francisco, CA 94107 (US). **DORAISWAMY, Anand**; 357 Tehama Street, Suite 1, San Francisco, CA 94103 (US). **CHRIST, Marie, Dvorak**; 650 Lombardy Lane, Laguna Beach, CA 92651 (US). **CHRIST, F., Richard**; 650 Lombardy Lane, Laguna Beach, CA 92651 (US).

(74) Agents: **AMII, Lisa, A.** et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).

(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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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,

*[Continued on next page]*

(54) Title: POLYMER FORMULATIONS FOR NASOLACRIMAL STIMULATION

(57) Abstract: Described herein are polymer formulations for facilitating electrical stimulation of nasal or sinus tissue. The polymer formulations may be hydrogels that are prepared by a UV cross-linking process. The hydrogels may be included as a component of nasal stimulator devices that electrically stimulate the lacrimal gland to improve tear production and treat dry eye. Additionally, devices and methods for manufacturing the nasal stimulators, including shaping of the hydrogel, are described herein.

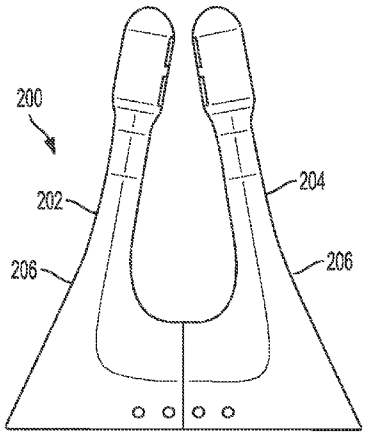


FIG. 2

WO 2015/130707 A3

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).

**Published**:

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

**(88) Date of publication of the international search report**:
26 November 2015

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/17379

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/14 (2015.01)
CPC - A61K 9/204; A61K 47/34; A61K 9/0024
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)
CPC (A61K9/204; A61K47/34; A61K9/0024; Y10S525/937; Y10S525/936; Y10S524/916; A61L31/145; C09J9/02; A61H23/0245; A61H2201/0153; A61H23/0263; A61H23/0218; A61H21/00; A61H9/0071; A61H23/02; A61M16/0672; A61M16/0666; A61M16/0688

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC (424/486; 424/484; 424/492; 522/1; 607/53; 428/500; 524/916; 351/159.61; 204/291; 607/41; 607/2; 607/115; 128/207.18; 607/39; 607/40; 600/391; 607/149; 252/500; 607/152; 607/153; 514/944; 526/246; 523/106; 524/520; 524/544; 351/159.33; 526/264; 526/347.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents/Scholar - Terms: hydrogel nasal stimulator monomer photoinitiator first second conductive electrical acrylate device resistivity maximum hydration-level tensile-strength Young's-modulus glass-transition-temperature cross-link density dry-eye polymer hydrated elongation break failure relative-humidity propylene-glycol hydroph

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2005/0137276 A1 (YAHIAOUI et al.) 23 June 2005 (23.06.2005)<br>para [0007], [0011], [0013], [0032], [0033], [0052], [0140]; abstract; title | 1-35, 74 and 99-101 |
| Y | WO 2012/139063 A2 (ACKERMANN et al.) 11 October 2012 (11.10.2012)<br>para [0003], [0009], [0029], [0113]-[0114], [0120], [0179]; figures 27D and 42B; abstract | 1-35, 74 and 99-101 |
| Y | US 2004/0151930 A1 (ROUNS et al.) 05 August 2004 (05.08.2004)<br>para [0037]-[0040] | 5 and 6 |
| Y | US 2011/0275734 A1 (SCALES et al.) 10 November 2011 (10.11.2011)<br>para [0088], [0160]; abstract | 9-10 |
| Y | US 5,800,685 A (PERRAULT) 01 September 1998 (01.09.1998)<br>col 3, ln 17-30 | 12-24 |
| Y | US 5,498,681 A (ASKARI et al.) 12 March 1996 (12.03.1996)<br>col 1, ln 57-63; col 3, ln 38-50 | 18 |
| Y | US 2009/0099600 A1 (MOORE et al.) 16 April 2009 (16.04.2009)<br>para [0009], [0026], [0029] | 19-20 |
| Y | US 2006/0018872 A1 (TEW et al.) 26 January 2006 (26.01.2006)<br>para [0012], [0018], [0021] | 21-22 |

☒ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 5 July 2015 (05.07.2015) | 24 JUL 2015 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (January 2015)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/17379

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2002/0049290 A1 (VANDERBILT) 25 April 2002 (25.04.2002)<br>para [0018] | 23 |
| Y | US 2013/0065765 A1 (SELIFONOV et al.) 14 March 2013 (14.03.2013)<br>para [0053], [0054] | 24 |
| Y | US 2010/0152708 A1 (LI et al.) 17 June 2010 (17.06.2010)<br>para [0121], [0158]; abstract | 27-28 |
| Y | US 2007/0237825 A1 (LEVY et al.) 11 October 2007 (11.10.2007)<br>para [0022], [0049]; abstract; claims 30-31 | 29-35 |
| Y | WO 2010/099818 A1 (ALINI et al.) 10 September 2010 (10.09.2010)<br>pg 1, ln 21-25; pg 6, ln 23-26; pg 8, ln 5-11; pg 13, ln 24-34; abstract | 99-101 |
| A | US 2013/0270491 A1 (PARK et al.) 17 October 2013 (17.10.2013)<br>para [0012], [0013], [0069]; table 2 | 1 and 74 |
| A | US 2011/0313330 A1 (LOUSHIN et al.) 22 December 2011 (22.12.2011)<br>para [0105], [0058]; figure 5; abstract | 1 and 74 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/17379

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

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

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

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

This International Searching Authority found multiple inventions in this international application, as follows:
---please see supplemental box --

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-35, 74 and 99-101

**Remark on Protest**

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

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

☐ No protest accompanied the payment of additional search fees.

BOX III: lack of unity
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-35, 74 and 99-101, directed a nasal stimulator device, where the electrically conductive hydrogel has one or more characteristics that adapt it for use with a nasal stimulator device.

Group II: Claims 36-60, directed to producing cross-linked, electrically conductive hydrogel.

Group III: Claims 61-73, directed a method for stimulating a lacrimal gland.

Group IV: Claims 75-91, directed to a method of manufacturing a nasal stimulator device comprising shaping a hydrogel in a tip assembly of the device.

Group V: Claims 92-98, directed to a method of improving electrical contact between an electrode of a nasal stimulator device and a nasal or sinus tissue.

The inventions listed as Group I-V do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Feature:

Group I does not require molding or shaping the formulation; and irradiating the formulation with UV radiation to cross-link the formulation, as required by Group II.
Group II does not require a nasal stimulator device; a reusable housing; a disposable component removably attached to the reusable housing and comprising an arm having a distal end that extends from the reusable housing when attached thereto; an electrode disposed within the arm; and the electrically conductive hydrogel at the distal end of the arm; and the electrically conductive hydrogel has one or more characteristics that adapt it for use with a nasal stimulator device, as required by Group I.

Group I does not require stimulating a lacrimal gland; placing an arm of a nasal stimulator device against a nasal or a sinus tissue, and activating the nasal stimulator device to provide electrical stimulation to the nasal or the sinus tissue, wherein the electrically conductive hydrogel is used to facilitate an electrical connectionbetween the nasal stimulator device and the nasal or the sinus tissue, as required by Group III.

Group III does not require a reusable housing; a disposable component removably attached to the reusable housing; the arm's distal end extends from the reusable housing when attached thereto; an electrode disposed within the arm; wherein the electrically conductive hydrogel comprises a first monomer; a second monomer; and a photoinitiator, and wherein the first monomer is an acrylate monomer and the electrically conductive hydrogel has one or more characteristics that adapt it for use with a nasal stimulator device, as required by Group I.

Group I does not require shaping a hydrogel in a tip assembly of the device and attaching the tip assembly to a base unit of the device, as required by Group IV.

Group IV does not require a reusable housing; a disposable component removably attached to the reusable housing and comprising an arm having a distal end that extends from the reusable housing when attached thereto; an electrode disposed within the arm; and an electrically conductive hydrogel at the distal end of the arm wherein the electrically conductive hydrogel comprises a first monomer; a second monomer; and a photoinitiator, and wherein the first monomer is an acrylate monomer and the electrically conductive hydrogel has one or more characteristics that adapt it for use with a nasal stimulator device, as required by Group I.

Group I does not require improving electrical contact between an electrode of a nasal stimulator device and a nasal or sinus tissue comprising manufacturing a hydrogel and creating a hydrophilic surface on the hydrogel, wherein the hydrophilic surface is created by treating the hydrogel with a low pressure plasma, depositing a hydrophilic polymer on the hydrogel using plasma polymerization, subjecting the hydrogel to aqueous sodium hydroxide, or adding a surfactant to the hydrogel during its formulation, as required by Group V.

Group V does not a reusable housing; a disposable component removably attached to the reusable housing and comprising an arm having a distal end that extends from the reusable housing when attached thereto; an electrode disposed within the arm; and an electrically conductive hydrogel at the distal end of the arm wherein the electrically conductive hydrogel comprises a first monomer; a second monomer; and a photoinitiator, and wherein the first monomer is an acrylate monomer and the electrically conductive hydrogel has one or more characteristics that adapt it for use with a nasal stimulator device, as required by Group I.

Group II does not require stimulating a lacrimal gland; placing an arm of a nasal stimulator device against a nasal or a sinus tissue, and activating the nasal stimulator device to provide electrical stimulation to the nasal or the sinus tissue, wherein the electrically conductive hydrogel is used to facilitate an electrical connection between the nasal stimulator device and the nasal or the sinus tissue, as required by Group III.

Group III does not require a cross-linked, electrically conductive hydrogel produced by mixing a first monomer, a second monomer, and a photoinitiator to prepare a formulation, wherein the first monomer is an acrylate monomer; molding or shaping the formulation; and irradiating the formulation with UV radiation to cross-link the formulation, as required by Group II.

Group II does not require shaping a hydrogel in a tip assembly of the device and attaching the tip assembly to a base unit of the device, as required by Group IV.

—please see next supplemental box —

—please see next supplemental box —
Group IV does not require a cross-linked, electrically conductive hydrogel produced by mixing a first monomer, a second monomer, and a photoinitiator to prepare a formulation, wherein the first monomer is an acrylate monomer; molding or shaping the formulation; and irradiating the formulation with UV radiation to cross-link the formulation, as required by Group II.

Group II does not require improving electrical contact between an electrode of a nasal stimulator device and a nasal or sinus tissue comprising manufacturing a hydrogel and creating a hydrophilic surface on the hydrogel, wherein the hydrophilic surface is created by treating the hydrogel with a low pressure plasma, depositing a hydrophilic polymer on the hydrogel using plasma polymerization, subjecting the hydrogel to aqueous sodium hydroxide, or adding a surfactant to the hydrogel during its formulation, as required by Group V.

Group V does not require a cross-linked, electrically conductive hydrogel produced by mixing a first monomer, a second monomer, and a photoinitiator to prepare a formulation, wherein the first monomer is an acrylate monomer; molding or shaping the formulation; and irradiating the formulation with UV radiation to cross-link the formulation, as required by Group II.

Group III does not require shaping a hydrogel in a tip assembly of the device and attaching the tip assembly to a base unit of the device, as required by Group IV.

Group IV does not require stimulating a lacrimal gland comprising: placing an arm of a nasal stimulator device against a nasal or a sinus tissue, the arm having a distal end and an electrically conductive hydrogel disposed at the distal end; and activating the nasal stimulator device to provide electrical stimulation to the nasal or the sinus tissue, wherein the electrically conductive hydrogel is used to facilitate an electrical connection between the nasal stimulator device and the nasal or the sinus tissue as required by Group III.

Group III does not require improving electrical contact between an electrode of a nasal stimulator device and a nasal or sinus tissue comprising manufacturing a hydrogel and creating a hydrophilic surface on the hydrogel, wherein the hydrophilic surface is created by treating the hydrogel with a low pressure plasma, depositing a hydrophilic polymer on the hydrogel using plasma polymerization, subjecting the hydrogel to aqueous sodium hydroxide, or adding a surfactant to the hydrogel during its formulation, as required by Group V.

Group V does not require stimulating a lacrimal gland comprising: placing an arm of a nasal stimulator device against a nasal or a sinus tissue, the arm having a distal end and an electrically conductive hydrogel disposed at the distal end; and activating the nasal stimulator device to provide electrical stimulation to the nasal or the sinus tissue, wherein the electrically conductive hydrogel is used to facilitate an electrical connection between the nasal stimulator device and the nasal or the sinus tissue, as required by Group III.

Group IV does not require improving electrical contact between an electrode of a nasal stimulator device and a nasal or sinus tissue comprising manufacturing a hydrogel and creating a hydrophilic surface on the hydrogel, wherein the hydrophilic surface is created by treating the hydrogel with a low pressure plasma, depositing a hydrophilic polymer on the hydrogel using plasma polymerization, subjecting the hydrogel to aqueous sodium hydroxide, or adding a surfactant to the hydrogel during its formulation, as required by Group V.

Group V does not require shaping a hydrogel in a tip assembly of the device and attaching the tip assembly to a base unit of the device, as required by Group IV.

Common Technical Features:

Group I and II share the technical feature of a first monomer; a second monomer; and a photoinitiator, wherein the first monomer is an acrylate monomer; and an electrically conductive hydrogel. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by US 2013/0270491 A1 to Park et al. (hereinafter Park). Park teaches a first monomer; a second monomer; and a photoinitiator, wherein the first monomer is an acrylate monomer; and an electrically conductive hydrogel (para [0012], [0013], [0069]; table 2 - a monomer, such as 3-sulfopropyl acrylate potassium salt; another monomer, such as acrylic acid; a photoinitiator; and to provide a conductive hydrogel; and conductivity of different samples are shown in table 2).

Group I and III share the technical feature of a nasal stimulator device; and an arm having a distal end and an electrically conductive hydrogel disposed at the distal end. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by US 2011/0313330 A1 to Loushin et al. (hereinafter Loushin). Loushin teaches a nasal stimulator device; and an arm having a distal end and an electrically conductive hydrogel disposed at the distal end (abstract; para [0105], [0058]; figure 5 – a device is provided for stimulating select body tissues and organs; for example, the device can be used to treat choanal atresia by dilating and electrically stimulating/cauterizing intranasal/sinus tissue; and electrically conductive hydrogels can be used as the conducting gel 517; and the arm would be tube 502; and the conducting gel is at one distal end of the tube 502).

Group I and IV share the technical feature of a nasal stimulator device. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated Loushin. Loushin teaches a nasal stimulator device (abstract; para [0105]; figure 5 – a device is provided for stimulating select body tissues and organs; for example, the device can be used to treat choanal atresia by dilating and electrically stimulating/cauterizing intranasal/sinus tissue).

Group I and V share the technical feature of a nasal stimulator device; and hydrogel. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by Loushin. Loushin teaches a nasal stimulator device; and hydrogel (abstract; para [0105], [0058]; figure 5 – a device is provided for stimulating select body tissues and organs; for example, the device can be used to treat choanal atresia by dilating and electrically stimulating/cauterizing intranasal/sinus tissue; and electrically conductive hydrogels can be used as the conducting gel in the device).

—please see next supplemental box —

—please see next supplemental box —

Group II and III share the technical feature of an electrically conductive hydrogel. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated Park. Park teaches an electrically conductive hydrogel (para [0013], [0069]; table 2 - a conductive hydrogel; and conductivity of different samples are shown in table 2).

Group II and IV share the technical feature of a hydrogel. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated Park. Park teaches a hydrogel (para [0013] - a conductive hydrogel).

Group II and V share the technical feature of hydrogel. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated Park. Park teaches a hydrogel (para [0013] - a conductive hydrogel).

Group III and IV share the technical feature of a nasal simulator device; and hydrogel. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by Loushin. Loushin teaches a nasal stimulator device; and hydrogel (abstract; para [0105], [0058]; figure 5 – a device is provided for stimulating select body tissues and organs; for example, the device can be used to treat choanal atresia by dilating and electrically stimulating/cauterizing intranasal/sinus tissue; and electrically conductive hydrogels can be used as the conducting gel in the device).

Group III and V share the technical feature of a nasal simulator device; and hydrogel. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by Loushin. Loushin teaches a nasal stimulator device; and hydrogel (abstract; para [0105], [0058]; figure 5 – a device is provided for stimulating select body tissues and organs; for example, the device can be used to treat choanal atresia by dilating and electrically stimulating/cauterizing intranasal/sinus tissue; and electrically conductive hydrogels can be used as the conducting gel in the device).

Group IV and V share the technical feature of a nasal simulator device; and hydrogel. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by Loushin. Loushin teaches a nasal stimulator device; and hydrogel (abstract; para [0105], [0058]; figure 5 – a device is provided for stimulating select body tissues and organs; for example, the device can be used to treat choanal atresia by dilating and electrically stimulating/cauterizing intranasal/sinus tissue; and electrically conductive hydrogels can be used as the conducting gel in the device).

Groups I-V share the technical feature of a hydrogel. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated Park. Park teaches a hydrogel (para [0013] - a conductive hydrogel).

As the shared technical features were known in the art at the time of the invention, they cannot be considered common technical features that would otherwise unify the groups. Therefore, Groups I-V lack unity under PCT Rule 13.