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(71) Demandeur/Applicant:
ARGOSE,INC., US

(72) Inventeurs/Inventors:
FREEMAN, JENNY, US;
MANSFIELD, JAMES, US;
PIERCE, ANDREA, US;
TREPAGNIER, PIERRE, US;
HOPMEIER, MICHAEL J., US

(74) Agent: MBM & CO.

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(54) Title: INTERFACE MEDIUM FOR TISSUE SURFACE PROBE

(57) Abrégé/Abstract:
A composition useful as an interface medium to optically couple and facilitate contact between a probe and a tissue surface, such as skin, is described. Compositions of the present invention have an index of refraction of approximately 1.4, which approximates the indices of both the skin and the probe, and may be clear in the spectral region of 270-500 nm, pH buffered, slippery, water soluble and viscous. The compositions may also be used to calibrate the application of pressure between a probe and a surface and standardize operation of the instrument, or adjust the surface to optimize use of the instrument.

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(71) Applicant *(for all designated States except US)*: **ARGOSE, INC.** [US/US]; 230 Second Avenue, Waltham, MA 02451 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FREEMAN, Jenny** [US/US]; 405 Concord Road, Weston, MA 02493 (US). **MANSFIELD, James** [CA/US]; 22-25 Peterborough Street, Boston, MA 02215 (US). **PIERCE, Andrea** [US/US]; 90 Jewett Lane, Hollis, NH 03049 (US). **TREPAGNIER, Pierre** [US/US]; 150 Brooks Street, Medford, MA 02155 (US). **HOPMEIER, Michael, J.** [US/US]; Suite A, 425 East Hollywood Boulevard, Mary Ester, FL 32580 (US).

(74) Agents: **REMENICK, James** et al.; Brobeck, Phleger & Harrison LLP, 1333 H. Street, N.W., Washington, DC 20005 (US).

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(54) Title: INTERFACE MEDIUM FOR TISSUE SURFACE PROBE

(57) Abstract: A composition useful as an interface medium to optically couple and facilitate contact between a probe and a tissue surface, such as skin, is described. Compositions of the present invention have an index of refraction of approximately 1.4, which approximates the indices of both the skin and the probe, and may be clear in the spectral region of 270-500 nm, pH buffered, slippery, water soluble and viscous. The compositions may also be used to calibrate the application of pressure between a probe and a surface and standardize operation of the instrument, or adjust the surface to optimize use of the instrument.

INTERFACE MEDIUM FOR TISSUE SURFACE PROBE

Background of the Invention

1. Field of the Invention

This invention relates to compositions useful as interface media for facilitating contact between a surface and a probe and to methods for using these compositions, and, in particular, to interface media for optically coupling, standardizing, and improving contact between a tissue surface, such as skin, and a probe being used to collect fluorescence or another desired spectra from the tissue.

2. Description of Background

Commercial spectrofluorometer products are available for taking skin fluorescence spectra (e.g. the Instruments S.A. SkinSkan). These devices are typically used in the cosmetics industry and often involve a fiber optic probe, which is simply pressed against the skin. However, bringing the fiber optic probe into simple direct contact with the skin has various disadvantages.

The surface of the skin is not perfectly smooth, but contains small hills and valleys, due, for example, to pores, wrinkles, hair follicles, and other surface irregularities. These irregularities can lead to small air pockets between the probe and the skin surface. Although the fiber optic probe and skin often share similar indices of refraction, both are significantly higher than air. Thus, the presence of air pockets may lead to additional scattering due to index mismatch at the probe/air and air/skin interfaces. These effects can induce higher variation in the spectra than would otherwise be the case, causing unnecessary noise.

In addition, the wide variation between the skin of different individuals causes the presence of air pockets and index mismatch to vary significantly between individuals. This leads to variation in the spectra and noise depending on the state of the individual's skin, making data interpretation more difficult. Finally, non-repeatable pressure and mechanical shear and torque forces are likely with the use of a dry fiber optic probe on skin, resulting in other non-repeatable effects.

Various oils and lubricants have been used to optimize optical properties for microscopy, see U.S. Patent Nos. 3,929,667; 4,526,711; 5,354,825; 5,480,723; and 5,667,840. Glycerol has been used experimentally as an interface medium in acquiring spectra of mucous membranes, specifically for research programs aimed at early detection of cancer of the cervix using fluorescence spectra, see, for example PCT Patent Application No. US99/07565; and U.S. Patent Nos. 5,601,079 and 5,341,805. However, there is currently a need for an interface medium that optimizes optical coupling between a tissue surface, such as skin, and a probe. This optical coupling agent would enhance both the transfer of light from the probe to the tissue, and the collection of light, such as fluorescence spectra, from the tissue to the probe.

Summary of the Invention

The present invention overcomes the problems and disadvantages associated with current strategies and designs and provides compositions useful as interface media to optically couple and facilitate contact between a probe and a tissue surface, such as skin. Compositions of the invention may also be used for calibration, such as calibrating the application of pressure between a probe and a surface, standardization such as standardizing the spectral output (e.g. fluorescence, infrared, thermal, or visible) of the instrument, or both, or to alter the metabolism, physiology, chemical, or other state of the tissue or surface.

Accordingly, one embodiment of the invention is directed to a composition for optically coupling a surface to a probe, comprising a viscous material having an index of refraction which approximates both the index of refraction of the surface and the index of refraction of the probe. Preferably, the index of refraction of the material is approximately 1.4. The material may be a liquid or gel and is preferably clear in the spectral region of 270-500 nm, water soluble, non-toxic, and pH buffered.

Another embodiment is directed to an improved method for measuring fluorescence emitted from a tissue surface comprising coupling a probe to the tissue surface using a composition according to the present invention and measuring fluorescence collected by the probe.

Another embodiment is directed to a method for optically coupling a surface to a probe comprising applying a composition according to the present invention to either the surface or probe or both, and bringing the surface, probe and composition into contact with each other.

Another embodiment is directed to a method for calibrating the pressure applied by a probe to a tissue surface comprising disposing a composition containing a fluorescent or phosphorescent dye between the probe and the tissue surface, applying pressure to the tissue surface with the probe causing at least a portion of the composition between the probe and tissue surface to thin out or disperse, exciting the dye in the composition which remains between the probe and tissue surface, and measuring excitation of the dye.

Other embodiments and advantages of the invention are set forth in part in the description which follows, and in part, will be obvious from this description, or may be learned from the practice of the invention.

Description of the Invention

As embodied and broadly described herein, the present invention is directed to the measurement of fluorescence spectra on the skin or other tissue using a novel composition which optimizes coupling of the tissue surface to the probe. More specifically, the present invention relates to compositions useful as an interface media between the fiber optic probe and skin, for the purpose of taking more accurate and repeatable spectra.

Compositions according to the present invention preferably comprise a viscous material or medium, such as a liquid, paste or gel, having an index of refraction that matches or approximates the indices of both the tissue surface and the probe which may be, for example, a simply quartz fiber (i.e. fused silica) probe. "Probe" or "optical probe" denote the optical train used to bring light to, and collect light from, the tissue sample. The probe is made up of optical fibers, but it may contain other refractive and reflective optical elements. Tissue surfaces are preferably skin surfaces but may also include the surface of mucus membranes or other surfaces of the body that can be easily contacted with the probe and, preferably, non-invasively contacted. Preferably, the

index of refraction is between 1.1 and 2.0, more preferably between 1.2 and 1.8 and even more preferably 1.4. The medium is preferably clear in the visible spectral region of 400 – 700 nm, more preferably in the region of 270 - 500 nm, and may be pH buffered; non-toxic, for example, not substantially toxic at the concentration being used to the organism on which the composition is being administered; or both.

The medium of the present invention allows for improved probe-to-tissue contact, even in the presence of dry skin, scaling skin, or air pockets due to skin texture, or other irregularities such as pits in the nail bed. The medium minimizes subject-to-subject variability, or site-to-site variability on a human subject, based on skin differences such as pigmentation, hair density, thickness, blood flow, and like physiological variables. The medium is preferably slippery, allowing for reduced friction and mechanical stress between the skin and probe. Further, accuracy and reproducibility are enhanced by providing improved thermal contact between the skin and the probe. This thermal buffering stabilizes and increases the thermal stability of the interface. In addition, an interface medium may contain one or more pharmaceutical agents that, upon application to the tissue, introduce therapeutically effective amounts of the pharmaceutical to the local environment. An interface medium may contain, for example, an effective amount of a pharmaceutical agent that modifies or stabilize local tissue perfusion or metabolism, or other aspects of the tissue environment. Stabilization or control of the local environment augments and improves data acquisition.

The medium is preferably water soluble for ease of application and removal and may be non-staining, but in some applications may be water insoluble. In one preferred embodiment, the medium comprises as the principal component an optically inactive ingredient, i.e., substantially inert and substantially transparent to allow the transfer of light with no more than negligible interference, for example, glycerin, polyethylene glycol such as, for example, most any PEG such as PEG-200, PEG-400 or PEG-600, polypropylene glycol, phosphate or combinations of these ingredients, and one or more buffers and/or wetting agents. Additional secondary components include PEG-150 stearate or distearate, glyceral stearate, cetyl alcohol or combinations thereof. Concentrations for the secondary components range from 0.01%

to 20%, preferably 0.1% to 10%, and more preferably 1% to 5%, and even more preferably 2%.

The present invention may be used in a variety of applications, including, but not limited to, human and veterinary medical and dental applications, forensic analysis, and other applications where spectral information is collected with a probe from a surface. An important feature of the present invention is its ability to be modified to serve as a calibrator of the amount of pressure used in measurement. Alternatively, the invention can be used as a standard which can serve as a basis for measuring the internal fluctuation in the components of the instrument, such as the wand. Ingredients that can be used include any optically responsive materials such as, for example, fluorescent, phosphorescent or bioluminescent ingredients, or combinations of such ingredients. The calibration function may be achieved, for example, by the addition of a small amount of optically active material to the medium such as, for example, a fluorescent or phosphorescent dye. Examples of optically active ingredients include, for example, fluorescein, acridine orange, 6-diamidino-2-phenylindole (DAPI), Hoechst 33358, cascade yellow, rhodamine and rhodamine derivatives such as rhodamine 6G, tetramethylrhodamine, rhodamine 800, 5-carboxyrhodamine 6G hydrochloride, lissamine rhodamine B sulfonal chloride and Texas Red sulfonyl chloride, azure (e.g. azure B), ethidium bromide, thiazole (e.g. thiazole orange), nile blue, Al phthalocyanine, Mag-Indo-1, oxazine, BIODIPY and its derivatives such as BIODIDY-FL, BIODIPY-R6G, BIODIPY-TMR, BIODIPY-581/591, BIODIPY-Texas Red, fluorescine (e.g. fura-red fluorescein), and combinations thereof (many of these chemicals are commercially available from Molecular Probes, Inc.). Preferably the optically active ingredient is soluble in the primary or secondary component of the medium which, in most cases, would require water solubility, but may require solubility in non-polar materials such as methanol, is insensitive to solvent polarity and pH variations, and is a dye with a useful fluorescence emission spectrum in the range of 450 nm to 750 nm, preferably between 500 and 700 nm, and more preferably between 550 nm and 650 nm.

The amount of the spectrally active component in the medium may vary considerably depending on the analytical equipment and the activity of the component itself. Preferred concentrations range from less than 0.0001% to more than 5%, preferably between 0.001% and 2%, and more preferably between 0.01% and 1%. Using this medium, the dye is excited by the spectrofluorometer. The spectrally active component of the medium may be passive or active, and produce a colormetric change or other spectral change that can be easily detected. Preferably, the active agent is a dye that fluoresces or phosphoresces in a benign (i.e. not relevant) spectral region. Alternately, its spectral response may be built into the analysis algorithm. Another embodiment is directed to a thermo-regulated medium that can be actively or passively thermo-regulated such as a crystal that breaks down or crystallizes in response to heat or spectral energy. Accordingly, the medium may be used to monitor or determine skin temperature.

Another embodiment is directed to a medium of the invention that is sterilized or sterilizable such that it can be used in a sterile environment or when sterile conditions are required. Alternatively, the interface medium may be packaged in a membrane or barrier (which may be bacteria permeable or impermeable) such that the surface to which it is applied does not contact the medium, but the membrane which may itself be sterile. Membranes such as paper; glass; plastic; polymers, such as nylon, Tyvec®, Teflon®; co-polymers of vinyliden chloride and vinyl chloride; and combinations thereof may be used to package the medium for specific applications such as in a glove or sleeve, or for further processing such as conventional sterilization. Preferably such membranes or barriers are clear to allow easy visualization and use of the medium without allowing passage of the ingredients through the barrier.

The invention may also serve as a standardization tool to standardize instruments used in surface spectral analysis, for example, see PCT Application No. US99/07565. Similar to the calibration modification, a small amount of fluorescent or phosphorescent dye is added to the medium such that the dye is excited by the spectrofluorometer or, alternatively, emits its own wavelength. In this manner, the instrument can be very precisely standardized. Of course, one modified medium or a

mixture of mediums can perform both calibration and standardization functions simultaneously.

In one application of the invention, a film of the medium is placed between the probe and skin. Increased probe/skin pressure causes the film to become thinner and hence the dye output to be less. By monitoring the dye's response, the spectrofluorometer insures optimum skin contact. The film may be applied in a number of ways, for example, by being impregnated into a foam so that it is squeezed out when pressure is applied, or by being otherwise encapsulated near the probe. In one embodiment, the intensity of returned light is indicative of the thickness of the film and, thus, the pressure being asserted against the skin. In addition to using the intensity of the returned light, the spectral location, i.e., wavelength, of the peak can be used to calibrate or otherwise standardize the instrument.

In addition to novel compositions, the present invention also is directed to novel methods of using the compositions of the present invention. One such embodiment is directed to a method for measuring fluorescence emitted from a tissue surface. This method comprises the steps of coupling a probe to the tissue surface using a composition according to the present invention and measuring fluorescence collected by the probe.

Another embodiment is directed to a method for optically coupling a surface to a probe comprising applying a composition according to the present invention to the surface or probe or both, and bringing the surface, probe and composition into contact with each other.

Another embodiment is directed to a method for reducing variability in the tissue, and particularly skin, by filling in and smoothing out surface irregularities by applying a composition according to the present invention to the surface.

Another embodiment is directed to a method for calibrating the pressure applied by a probe to a tissue surface comprising disposing the composition of the present invention between the probe and the tissue surface, applying pressure to the tissue surface with the probe causing at least a portion of the composition between the probe and tissue surface to disperse or thin out, exciting the dye in the composition

remaining between the probe and tissue surface, and measuring excitation of the dye. Excitation may be produced by the induced pressure or simply the increased heat of the living surface. In this manner, the composition may also be used as a standardization tool whereby the instrument or components of the instrument such as the optical cable of the wand are spectrally standardized.

Other embodiments and uses of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. All references cited herein for any reason, including all U.S. and foreign patents and patent applications, are specifically and entirely incorporated by reference. It is intended that the specification and examples be considered exemplary only, with the true scope and spirit of the invention indicated by the following claims.

CLAIMS

1. A composition for optically coupling a surface to a distal end of an optical probe comprising (i) a viscous material having an index of refraction that approximates both an index of refraction of the surface and an index of refraction of the distal end of the optical probe and (ii) a dye.

2. The composition of claim 1, wherein the viscous material comprises:

a) a principal component selected from the group consisting of glycerine, polyethylene glycol, polypropylene glycol, phosphate or any combination thereof; and

b) one or more secondary components selected from the group consisting of PEG-150 stearate or di-stearate, glyceral stearate, cetyl alcohol or any combination thereof.

3. The composition of claim 2, wherein the concentration of the secondary components range from 0.01% to 20%.

4. The composition of any preceding claim, wherein the dye fluoresces or phosphoresces in a benign spectral region when excited by a spectrophotometer.

5. The composition of claim 4, wherein the dye is selected from the group consisting of fluorescein, acridine orange, 6-diamidino-2-phenylindole, Hoechst 33358, cascade yellow, rhodamine, rhodamine derivatives, azure, ethidium bromide, thiazole, nile-blue, Al phthalocyanine, Mag-Indole-1, oxazine, BIODIPY and BIODIPY derivatives.

6. The composition of any preceding claim, wherein the index of refraction of the material is approximately 1.4.

7. A composition of any preceding claim, wherein the surface is skin or a mucosal surface of a patient.

8. A method for optical measurement from a tissue surface comprising:

a) optically coupling a distal end of a probe to the tissue surface with a composition according to any of claims 1 to 7; and

b) measuring the fluorescence or phosphorescence collected by the probe.

9. The method of claim 8, wherein the measurement is a pressure calibration and the method further comprises the step of applying pressure to the tissue surface with the probe causing at least a portion of the composition between the probe and the tissue surface to disperse.

10. The method of claim 8 or claim 9, wherein the tissue surface is skin or a mucus membrane.

11. The method of any of claims 8 to 10, wherein the optical probe comprises refractive and reflective optical elements.

12. The method of any of claims 8 to 11, further comprising the step of exposing the tissue surface with excitation from a spectrophotometer.

13. A method for calibrating pressure applied by a probe to a tissue surface comprising:

optically coupling a distal end of the probe to the tissue surface with a composition that according to any of claims 1 to 7; and

applying pressure to the tissue surface with the probe causing at least a portion of the composition between the probe and the tissue surface to disperse;

exciting the dye in the composition remaining between the probe and the tissue surface;

measuring excitation of the dye.

14. A package of a composition according to any one of claims 1 to 7.

15. The package of claim 14, comprising a membrane or barrier in which the composition is packaged.

16. The package of claim 15, wherein the membrane or barrier comprises a material selected from the group consisting of paper, glass; plastic; polymer, nylon, Tyvec™, Teflon™, and co-polymers of vinylidene chloride and vinyl chloride.

17. The package of any of claims 14 to 16, wherein the composition is a liquid, paste, gel, foam or film.

18. The package of claim 17, wherein the composition can in use be squeezed out when pressure is applied.

19. The package of any of claims 14 to 18 which is sterile.

20. The package of any of claims 14 to 19 for optically coupling a surface to a distal end of an optical probe.

21. The package of any of claims 1 to 20, wherein the film is an impregnated material having consistency such that application of pressure squeezes out the material.

22. The package of any of claims 14 to 20 wherein the film is an impregnated foam material.

23. The use of the composition of any of claims 1 to 7 as a surface-to-probe optical coupling medium.