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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 March 2011 (31.03.2011)

PCT

(10) International Publication Number
WO 2011/037533 A1

(51) International Patent Classification:
B32B 5/16 (2006.01) ***A61B 5/00*** (2006.01)
G01N 21/65 (2006.01) ***G01J 3/44*** (2006.01)
G01N 33/58 (2006.01)

(21) International Application Number:
PCT/SE2010/051031

(22) International Filing Date:
24 September 2010 (24.09.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0950702-1 25 September 2009 (25.09.2009) SE

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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, 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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,

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(54) Title: SERS DEVICE

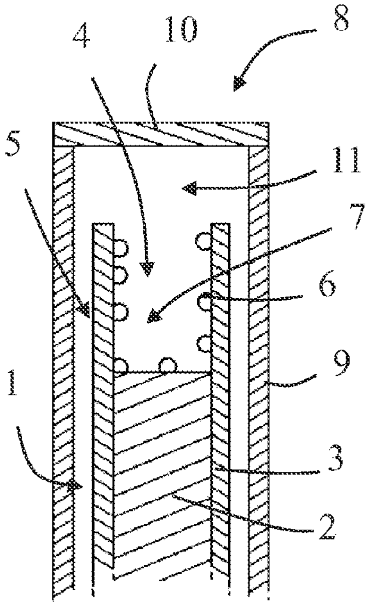

Fig. 3

(57) Abstract: The sensor device comprises an optical fiber (1) which at a first end comprises a SERS surface for surface enhanced Raman spectroscopy, and in a second end is configured for being connected to a Raman spectrometer. Preferably a fiber cladding (3) extends beyond the fiber core (2) at the first end, whereby a fiber core end and parts of the inner surface of the fiber cladding constitute inner walls of a cavity (4). Metal nanoparticles (6) are arranged on at least parts of the inner walls of said cavity (4). Optionally a sealing arrangement (8) radially surrounds and seals the optical fiber at said first end, whereby a space (11) is formed between the optical fiber (1) and the sealing arrangement (8). The sealing arrangement protects the SERS surface before use. The space (11) may be filled with a calibration solution, which can be used to acquire a calibration spectrum before opening of the sealing arrangement and analysis.

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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, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

SERS DEVICE

Technical field of the invention

The present invention relates to a sensor device for qualitative and quantitative analysis of organic and inorganic compounds using Raman spectroscopy, and in particular to such a sensor device using nanoparticles for Surface-Enhanced Raman Scattering (SERS).

Background of the invention

Raman spectroscopy is based on that monochromatic light, usually from a laser, interacts with a sample and due to inelastic scattering (Raman scattering) a fraction of the incident light is shifted in energy. Molecules can be detected by studying fingerprint type of spectra, i.e., complicated spectra with several peaks, collected from the scattered light. Raman spectroscopy also distinguishes and detects different functional groups in a molecule, such as -NO2, -COOH, -CN, etc. The main problem using a Raman spectrometer for detection of e.g. ultra low concentrations is a low sensitivity. In normal Raman spectroscopy only 1 out of 10^7 photons are Raman scattered.

Fortunately, the Raman scattering can be amplified as much as 10^3-10^{15} times by adsorption of compounds (or ions) on certain surfaces where surface-enhanced Raman scattering (SERS) occurs, which significantly improves sensitivity and molecular specificity. With SERS single molecules can be detected. The surface-enhanced Raman scattering is strongest on silver, but is observable on gold, copper, and palladium as well.

Surface-enhanced Raman scattering arises from two mechanisms. The first mechanism involves excitation of surface plasmons by incident light (surface plasmon resonance), which results in enhanced scattering due to an enhanced electric field produced at the surface of the metal. Molecules adsorbed or in close proximity to the surface experience an exceptionally large electromagnetic field. The second mechanism involves formation of a charge-transfer complex between the surface and an absorbed molecule i.e. the molecule to be analyzed or detected. In particular molecules with lone-pair electrons or [pi]-clouds show the strongest enhancement according to the second mechanism.

The enhancement of the SERS is dependent on the morphology of the metal surface. Atomically rough surfaces or nanoparticles with certain size, shape and distribution can be used to improve the strength of the enhancement. On single nanoparticles aggregates enhancement factors of 10^{14}-10^{15} have been demonstrated. However, large surfaces with controllable particle size, shape and distribution, which enables detection of even lower detection levels is a challenge.

SERS analysis is commonly performed in controlled environments in order to avoid contaminants that would give interfering Raman scattering that limits the sensitivity. In particular, quantitative analysis requires stable conditions or else elaborate calibrations have to be performed. The sample is typically placed in a sample chamber and illuminated by a laser beam. Scattered light is collected by a probe that is placed at an angle to the path of the laser beam and transmitted to a Raman spectrometer.

Optical fibers can be used in different ways for SERS analysis. In addition to transmission of laser light and transmission of scattered light to the Raman spectrometer, part of the optical fibers can also be used as SERS substrates. Thereby a versatile sensor head with direct optical connection to a transmission line to the Raman spectrometer is obtained. Optical fibers with tapered tips or hollow fibers have been suggested in order to increase the SERS surface and hence to improve the SERS signal. In the international patent application WO 2009/031033 a liquid core photonic crystal fiber is used to increase the area. Further silver nanoparticles may be deposited on inner walls of the liquid core photonic crystal fiber or on the tip of a multimode fiber in order to form a SERS substrate, which is dipped into a sample solution with analyte molecules and silver nanoparticles. Analyte molecules then become sandwiched between deposited nanoparticles and nanoparticles from the solution, whereby a stronger SERS signal can be obtained.

When used in e.g. portable sensors or sensors to be used in harsh environments, contaminants and changes in environmental conditions cause severe problems. For example in *in vivo* testing, the SERS substrate is exposed to the atmosphere before entering a totally different environment, i.e. a body fluid of a human body, where different constituents of the body fluid may be obstructive for SERS analysis.

Summary of the invention

In view of the foregoing, it is an object of the present invention to provide a sensor device for improved SERS analysis, e.g. *in vivo* or *in vitro* analysis.

In a first aspect of the invention a sensor device for qualitative and/or quantitative analysis of organic and/or inorganic compounds is provided. The sensor device comprises an optical fiber which at a first end comprises metal nanoparticles for surface enhanced Raman spectroscopy, and in a second end is configured for being connected to a Raman spectrometer. The optical fiber comprises a fiber cladding with a fiber cladding end, which fiber cladding end is located at the first end, and a fiber core with a fiber core end, which fiber core end is located at the first end, the fiber cladding being arranged to radially surround said fiber core with an inner surface of the fiber cladding contacting an outer surface of the fiber core. The fiber cladding end extends longitudinally beyond the fiber core end, whereby said fiber core end and parts of the inner surface of the fiber cladding constitute inner walls of a cavity. Further, a cavity opening is defined by the fiber cladding end. Metal nanoparticles are arranged on at least parts of the inner walls of said cavity.

In a second aspect of the invention a sealing arrangement for a sensor device is provided. The sensor device comprises an optical fiber, which at a first end comprises metal nanoparticles forming a SERS surface for surface enhanced Raman spectroscopy and in a second end is configured for being connected to a Raman spectrometer. The sealing arrangement radially surrounds and seals the optical fiber at said first end, whereby a space is formed between the optical fiber and the sealing arrangement. The sealing arrangement protects the SERS surface before use. Preferably said space comprises a calibration solution, which can be used to acquire a calibration spectrum. The sealing arrangement, or at least a septum thereof, is adapted to be punctured or opened before analysis.

Thanks to the invention it is possible to perform qualitative and quantitative analysis of organic and inorganic compounds with high sensitivity.

It is a further advantage of the invention to provide a sensor device that is simple to use. The sensor head may during storage, transport and insertion into the environment where analysis is to be performed be protected by the sealing arrangement until a user decides to start the testing by simply ejecting the optical fiber from the sealing arrangement or by other means open or puncture the sealing arrangement. Quantitative measurement may be simplified since the first end of the optical fiber and hence the sensitive SERS surface may be stored in a controlled environment, such as a calibration solution, until testing. When still in the calibration solution the sensor device will generate a stable signal serving as a reference. Ejection of the optical fiber will lead to a change in signal, which immediately can be compared to the stored reference, whereby at least a relative concentration compared to the concentration of the calibration solution can be deduced.

It is a yet further advantage of the invention to provide a reliable sensor device. Since the optical fiber that is intended to transmit the scattered light to a Raman spectrometer also forms at least part of the SERS surface there are only a few parts of the device. Also the analysis cavity and an optional filter provide a sheltered position for the nanoparticles, and hence unwanted constituents of the analyte, for instance a body fluid, may be kept away.

Embodiments of the invention are defined in the dependent claims. Other objects, advantages and novel features of the invention will become apparent from the following detailed description of the invention when considered in conjunction with the accompanying drawings and claims.

Brief description of the drawings

Preferred embodiments of the invention will now be described with reference to the accompanying drawings, wherein

Fig. 1 schematically illustrates a sensor device comprising a SERS cavity according to the invention

Fig. 2 schematically illustrates a sensor device comprising a meshwork according to the invention;

Fig. 3 schematically illustrates a sensor device according to Fig. 1 provided with a sealing arrangement according to the invention; and

Fig. 4 schematically illustrates a sensor device comprising a SERS tip provided with a sealing arrangement according to the invention.

Detailed description of embodiments

Referring to Figs. 1-3, a sensor device according to the invention comprises an optical fiber 1, which at a first end comprises a SERS surface, preferably with metal nanoparticles 6, for surface enhanced Raman spectroscopy (SERS) and in a second end is configured for being connected to a Raman spectrometer. In use, the SERS surface in the first end has to be in physical contact with an analyte to be analyzed and in the second end in optical contact with a Raman spectrometer. The optical contact may be provided by the optical fiber, alone or in combination with one or more other optical fibers. Molecules from the analyte are adsorbed on the SERS surface. Excitation light for SERS analysis is transmitted through the optical fiber and scattered light propagate through the optical fiber to the Raman spectrometer, whereby a Raman spectra can be acquired. The design of the sensor device according to the invention makes it especially useful for *in vivo* analysis in extracellular fluids (or the blood) but it can of course be used in other analytes.

Preferably the optical fiber 1 at the first end comprises a fiber core 2 with a fiber core end and a fiber cladding 3 with a fiber cladding end, which fiber cladding 3 is arranged to radially surround said fiber core 2 with an inner surface of the fiber cladding 3 contacting an outer surface of the fiber core 2. The SERS surface 7 is at least partly formed by an exposed portion of the fiber core 2 at the first end 5.

Fig. 1 schematically illustrates one embodiment of a sensor device for qualitative and/or quantitative analysis of organic and/or inorganic compounds according to the present invention. The sensor device comprises an optical fiber 1 which at a first end comprises metal nanoparticles 6 for surface enhanced Raman spectroscopy, and in a second end is configured for being connected to a Raman spectrometer. In detail, the optical fiber 1 comprises a fiber cladding 3 being arranged to radially surround a fiber core 2 with an inner surface of the fiber cladding 3 contacting an outer surface of the fiber core 2. The fiber cladding 3 extends longitudinally beyond a fiber core end at the first end of the optical fiber 1, whereby an exposed surface of the fiber core end and an exposed part of the inner surface of the fiber cladding constitute inner walls of a cavity 4. A cavity opening is defined by a fiber cladding end at the first end of the optical fiber 1. Nanoparticles 6, preferably made of a metal or metal alloy, by way of example gold nanoparticles, are arranged on at least parts of the inner walls of said cavity 4 in order to form a SERS surface 7.

The fiber core preferably has a diameter of between 1-250 μm, more preferably between 1-80 μm, most preferably between 4-20 μm. For such fiber core diameters the fiber cladding end preferably extends 1-100 μm, more preferably 1-80 μm, most preferably 4-20 μm, longitudinally beyond the fiber core end.

Referring to Fig. 2, as an alternative or as a complement to the above described sensor surface formed on the inner walls of the cavity 4, the cavity 4 may comprise a three dimensional meshwork 12 of rods and/or tubes to which meshwork 12 said metal nanoparticles 6 are attached. Preferably the rods and/or tubes are made of a metal oxide, and more preferably they comprise zinc oxide.

The cavity 4 can optionally at its opening be delimited by a filter. The filter is preferably a biocompatible filter of the type described in the international patent application with publication number WO 2009/091311. A filter prevents unwanted constituents, such as blood cells, of the analyte (blood) to enter or to block the cavity 4.

The metal nanoparticles are preferably made of gold or silver, most preferably gold, however not limited to this. Suitable materials are gold, silver, palladium, copper, cadmium or any alloys thereof. The nanoparticles have sizes ranging from 5-500 nm, preferably 10-200 nm. The nanoparticles can also be functionalized by binding surfactants, e.g. organic molecules, antibodies or similar compound, to their surfaces. By providing the nanoparticles with surfactants, analytes, i.e. molecules, to be analyzed can be selectively attached to the nanoparticles by bridging to said surfactant. The selection of appropriate surfactants is based on the analyte which is to be analyzed and should be obvious to a person skilled in the art.

As mentioned the sensor device is sensitive to contaminants and changes in environmental conditions. The present invention provides a sealing arrangement 8 for a sensor device, wherein the sensor device comprises an optical fiber 1, which at a first end comprises metal nanoparticles 6 for surface enhanced Raman spectroscopy and in a second end is configured for being connected to a Raman spectrometer. The sealing arrangement 8 radially surrounds and seals the optical fiber 1 at said first end, whereby a space is formed between the optical fiber 1 and the sealing arrangement 8. A calibration solution can preferably be stored in the sealing device 8 during storage and before use.

The sealing arrangement 8 prevents contaminants from entering the cavity before use. Due to the sealing arrangement 8 of the present invention the SERS surface can be protected also during insertion of the sensor device into the analyte, for instance the human body. The sealing arrangement 8, or at least a septum thereof, is adapted to be punctured or opened before analysis.

In one embodiment of the invention, exposure of the optical fiber 1 to the analyte is enabled by a septum 10 adapted to be punctured, preferably by ejection of the optical fiber 1 from the sealing arrangement 10.

Fig.3 schematically illustrates one embodiment of a sensor device according to the present invention comprising a sealing arrangement 8 and an analysis cavity 7 as described above with reference to Fig. 1. The sensor device comprises an optical fiber 1, which at a first end comprises metal nanoparticles 6 for surface enhanced Raman spectroscopy, and in a second end is configured for being connected to a Raman spectrometer. The fiber cladding 3 of the optical fiber 1 extends longitudinally beyond the fiber core 2 of the optical fiber 1, whereby an exposed surface of the fiber core end and an exposed part of the inner surface of the fiber cladding 3 constitute inner walls of a cavity 4. A cavity opening is defined by the fiber cladding end at the first end of the optical fiber. The cavity opening is optionally covered by a filter. Metal nanoparticles 6, preferably gold nanoparticles, are arranged on at least parts of the inner walls of said cavity 4. A sealing arrangement 8 radially surrounds and seals the optical fiber 1 at said first end, whereby a space 11 is formed between the optical fiber 1 and the sealing arrangement 8. By way of example the sealing arrangement 8 comprises a tubular member 9, preferably a plastic or polymer tubular member, and a septum 10, wherein the septum 10 can be an integrated part of the tube 9 or a welded or by other means attached separate part.

The septum 10 of the sealing arrangement is adapted to be punctured or removed before use. Preferably the septum 10 is arranged to be punctured or removed by the optical fiber 1 when the optical fiber 1 is ejected from the sealing arrangement 8.

In one embodiment of the present invention a calibration solution is stored in the space 11 formed between the optical fiber 1 and the sealing arrangement 8. The calibration solution also fills the cavity 4. Thus the sensitive SERS surface is stored in a controlled environment. The calibration solution can be used to improve the SERS analysis. Without the protection offered by the sealing arrangement 8 the SERS surface would be exposed first to the atmosphere before being inserted into the analyte, e.g. the human body in an *in vivo* analysis. This change in environment would require a thorough calibration process to get a reliable result. By keeping the SERS surface in the calibration solution until the puncturing of the septum a calibration spectrum can be acquired. This spectrum can be used as a reference for quick and reliable analysis.

Accordingly a method of qualitative and/or quantitative analysis of organic and/or inorganic compounds in an analyte comprises the steps of:

- inserting the sensor device into the analyte;
- ejecting the optical fiber 1 through a septum 10 of a sealing arrangement 8 that radially surrounds and seals the optical fiber 1 at said first end;
- acquiring a calibration spectrum from a calibration solution, which calibration solution is enclosed in a space 11 between the optical fiber 1 and the sealing arrangement 8, before ejecting the optical fiber 1; and
- acquiring a Raman spectrum.

Although the sensor device with the sealing arrangement has been described with a SERS surface of cavity type, the sealing arrangement can be used for other designs. Fig. 4 schematically illustrates a sensor device comprising a sealing arrangement 8 that radially surrounds and seals an optical fiber 1 with a different core-cladding configuration, and consequently a different SERS surface geometry. The optical fiber 1 comprises a fiber core 2 with a fiber core end, and a fiber cladding 3 with a fiber cladding end. As illustrated in Fig. 4 an end portion of the fiber core extends longitudinally beyond the fiber cladding end, i.e. the fiber core protrudes from the fiber cladding, and an outer circumferential surface of the fiber core is exposed. Metal nanoparticles are arranged on the protruding end portion of the fiber core 2. A space 11 is formed between the protruding end portion and the sealing arrangement 8. Optionally the space is filled with a calibration solution.

In another embodiment of the present invention the fiber core end and the fiber cladding end are aligned and only a planar end surface of the fiber core is exposed, onto which metal nanoparticles are arranged in order to form a SERS surface. A space is formed between the planar end surface and the sealing arrangement.

The optical fiber of sensor devices according to the invention may have different length. The Raman spectrometer is typically an expensive device that is used for many tests, while the sensor device may be a replaceable part that is only used for single tests. Hence the optical fiber of the sensor device preferably comprises a connector for simple coupling to the Raman spectrometer.

It should be appreciated that the embodiments have been described with reference to a few basic designs and the drawings are not necessarily to scale. Other similar designs of the sensor device are possible in order to optimize the performance with respect to certain applications, such as to ensure a reproducible insertion of the sensor device into a human body. For example the end surface of the fiber core may have a different shape than planar, such as convex or concave, or being roughened. The protruding fiber cladding may also be cut at an angle, which may simplify the ejection of the optical fiber through the sealing arrangement. Moreover, the fiber cladding and the fiber core may be formed from a monolithic structure, e.g. by etching. The nanoparticles can have various shapes, such as elongated, spherical, cubic etc. The nanoparticles can also be sintered to form a continuous or semi-continuous roughened film.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiments, it is to be understood that the invention is not to be limited to the disclosed embodiments, on the contrary, it is intended to cover various modifications and equivalent arrangements within the appended claims.

CLAIMS

1. A sensor device for qualitative and/or quantitative analysis of organic and/or inorganic compounds, wherein the sensor device comprises an optical fiber (1) comprising a fiber core (2) and a cladding (3), wherein the optical fiber at a first end (5) comprises a SERS surface (7) for surface enhanced Raman spectroscopy, and in a second end is configured for being connected to a Raman spectrometer, **characterized in** that the sensor device further comprises a sealing arrangement (8) that radially surrounds and seals the optical fiber at said first end, whereby a space (11) is formed between the optical fiber (1) and the sealing arrangement (8), wherein the space (11) is at least partly filled with a calibration solution.

2. The sensor device according to claim 1, wherein the sealing arrangement (8) comprises a septum (10) arranged to be punctured or opened before analysis.

3. The sensor device according to claim 2, wherein the septum (10) is arranged to be punctured or opened by the optical fiber (1) when the optical fiber (1) is ejected from the sealing arrangement (8).

4. The sensor device according to any of the preceding claims, wherein the sealing arrangement (8) comprises a tubular member (9), preferably a plastic or polymer tubular member.

5. The sensor device according to claim 4, wherein a first end of the tubular member (9) is arranged to radially surround the optical fiber (1) and the septum (10) is attached to a second end of the tubular member (9).

6. The sensor device according to any of the preceding claims, wherein the fiber cladding (3) with a fiber cladding end, which fiber cladding end is located at the first end (5), and the fiber core (2) with a fiber core end, which fiber core end is located at the first end, the fiber cladding (3) being arranged to radially surround said fiber core (2) with an inner surface of the fiber cladding contacting an outer surface of the fiber core (2), the fiber cladding end extends longitudinally beyond the fiber core end, whereby said fiber core end and parts of the inner surface of the fiber cladding constitute inner walls of a cavity (4) and a cavity opening is defined by the fiber

cladding end, and the SERS surface (7) is formed on at least parts of the inner walls of said cavity (4).

7. The sensor device according to any one of claims 1 to 6, wherein the SERS surface is formed by metal nanoparticles (6) that are arranged on at least a part of the surface of the fiber core (2) and/or at least parts of the inner walls of said cavity (4).

8. The sensor device according to anyone of claims 6 or 7, wherein the cavity (4) comprises a three dimensional meshwork (12) of metal oxide rods and/or tubes to which meshwork metal nanoparticles (6) are attached.

9. The sensor device according to claim 8, wherein the metal oxide rods and/or tubes comprise zinc oxide.

10. The sensor device according to anyone of claims 6-9, wherein the first end (5) of the optical fiber comprises a filter which covers the cavity opening.

11. The device according to anyone of the preceding claims, wherein the fiber core has a diameter of between 1-250 µm, preferably between 1-80 µm, most preferred between 4-20 µm.

12. The device according to anyone of claims 6-11, wherein the fiber cladding end extends 1-100 µm, preferably 1-80 µm, most preferred 4-20 µm, longitudinally beyond the fiber core end.

13. Use of a sensor device as defined in anyone of claims 1 to 12 together with a Raman spectrometer for *in vivo* or *in vitro* analysis of inorganic and/or organic compounds.

14. Method of using a sensor device for qualitative and/or quantitative analysis of organic and/or inorganic compounds in an analyte together with a Raman spectrometer, the sensor device comprises an optical fiber (1), which at a first end comprises metal nanoparticles (6) for surface enhanced Raman spectroscopy and in a second end is configured for being connected to the Raman spectrometer, **characterized by** the steps of:
- inserting the sensor device in the analyte;
- ejecting the optical fiber (1) through a septum (10) of a sealing arrangement that

radially surrounds and seals the optical fiber at said first end; and
- acquiring a Raman spectrum.

15. Method according to claim 14, further comprising the step of acquiring a calibration spectrum from a calibration solution, which calibration solution is enclosed in a space (11) between the optical fiber (1) and the sealing arrangement (8), before ejecting the optical fiber (1).

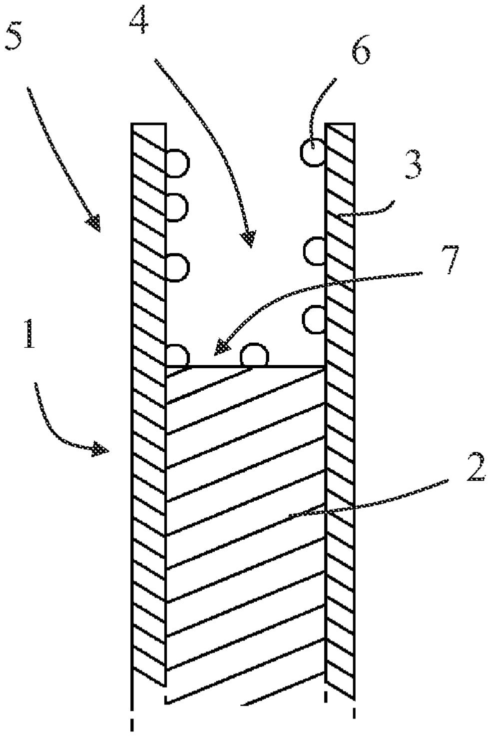

Fig. 1

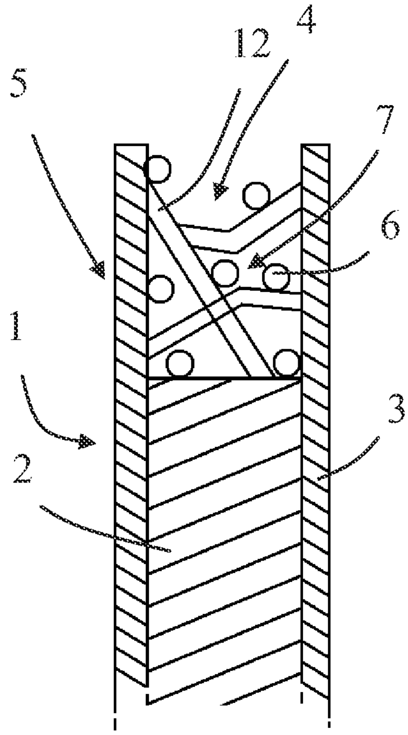

Fig. 2

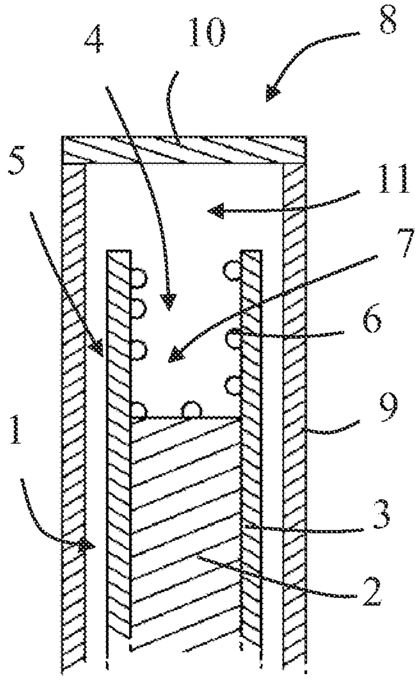

Fig. 3

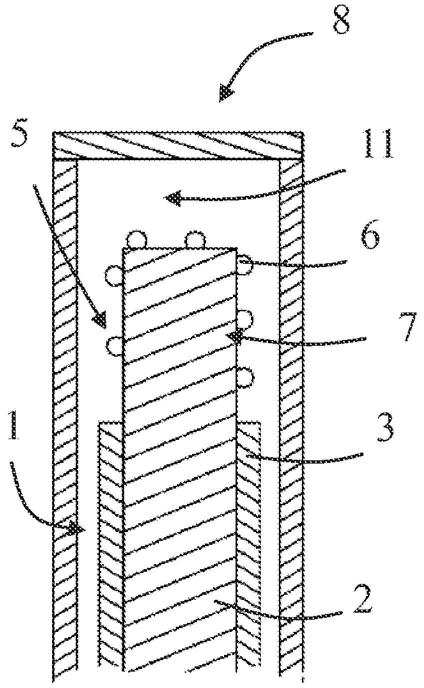

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/SE2010/051031

A. CLASSIFICATION OF SUBJECT MATTER
INV. B32B5/16 G01N21/65 G01N33/58 A61B5/00 G01J3/44
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B32B G01N A61B G01J

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, BIOSIS, WPI Data, INPSEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 864 397 A (VO-DINH TUAN [US]) 26 January 1999 (1999-01-26)	1-14
A	column 2, line 6 - line 63 column 3, line 65 - column 4, line 50 column 5, line 53 - column 9, line 12 figures 1A,6A-10C figures 13A-26 -----	15
A	WO 2009/031033 A2 (UNIV CALIFORNIA [US]; GU CLAIRE [US]; ZHANG YI [US]; SHI CHAO [US]; SE) 12 March 2009 (2009-03-12) figure 5 -----	1-15
A	WO 2009/091311 A1 (NANEXA AB [SE]; JOHANSSON ANDERS [SE]; ROOTH MAARTEN [SE]; BOMAN MATS) 23 July 2009 (2009-07-23) claim 1 ----- -/--	1-15

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

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search
7 January 2011

Date of mailing of the international search report
19/01/2011

Name and mailing address of the ISA/
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Authorized officer
Consalvo, Daniela

International application No
PCT/SE2010/051031

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE LIMA CARLOS J ET AL: "Catheters: instrumental advancements in biomedical applications of optical fibers", LASERS IN MEDICAL SCIENCE, vol. 24, no. 4, July 2009 (2009-07), pages 621-626, XP002615595, ISSN: 0268-8921 figure 1 -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/SE2010/051031

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5864397	A	26-01-1999	NONE		
WO 2009031033	A2	12-03-2009	CA 2698883	A1	12-03-2009
WO 2009091311	A1	23-07-2009	EP 2252389	A1	24-11-2010