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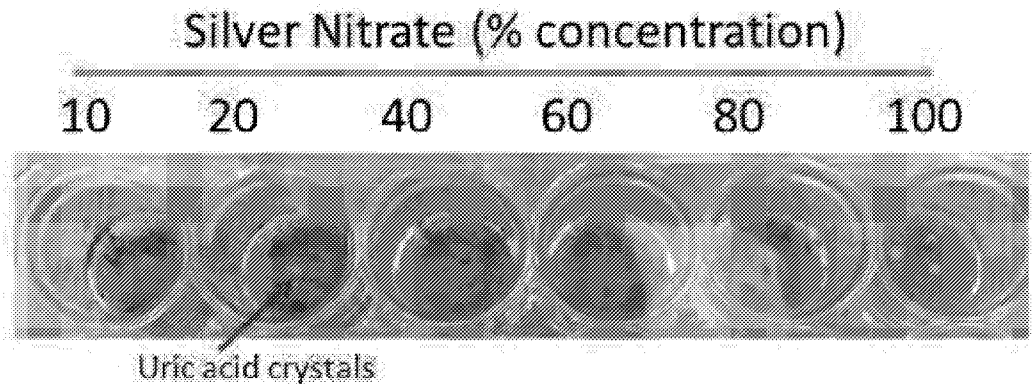

FIG. 1

(57) Abstract: The present disclosure is directed to a kit and methods for using the same. The kit includes a plate including at least one well, wherein the well includes a silver nitrate and a catalyst. The method includes providing a sample of synovial fluid to a well of a plate, wherein the well includes a silver nitrate and a catalyst and determining a presence of monosodium urate (MSU) crystals, wherein the presence of MSU crystals indicates that gout is detected in the sample.

WO 2018/209178 A1

METHOD AND KIT FOR DETERMINING THE PRESENCE OF MONOSODIUM URATE CRYSTALS IN JOINT SYNOVIAL FLUID

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims benefit of United States Provisional Applications 62/504,623 filed on May 11, 2017, the contents of both of which are incorporated by reference.

BACKGROUND OF THE DISCLOSURE

[0002] Gout is a form of arthritis that develops in some people who have high levels of uric acid in the blood. Uric acid can form needle-like crystals in joints and cause sudden, severe episodes of pain, tenderness, redness, warmth and swelling in joints. Pain and inflammation occur when too much uric acid crystallizes and deposits in the joints as monosodium urate crystals (MSU).

[0003] Gout has become more common in the United States in the past two decades, in part because of the nation's obesity crisis and a greater frequency of high blood pressure, new research indicates. Gout, a type of arthritis that occurs when uric acid crystals build up in the joints, was also found to be more common in men than in women. The condition now affects about 8.3 million people, or about 4% of the population. And the risk of getting gout increases with age. Gout, an inflammatory arthritis triggered by crystallization of uric acid inside the joints, causes swelling and severe pain. Gout can cause an attack of sudden burning pain, stiffness, and swelling in a joint, usually a big toe. These attacks can happen over and over unless gout is treated. Over time, they can harm joints, tendons, and other tissues.

[0004] To diagnose gout, physicians typically will take a patient's medical history, examine the affected joint and perform a blood test. A blood test to measure the level of uric acid in the

blood is the typical first step to diagnose gout. However, a high level of uric acid in the blood doesn't necessarily mean that the patient has gout, just as a normal level doesn't mean that the patient does not have gout. The physician also has to rule out other potential causes of joint pain and inflammation such as infection, injury or another type of arthritis. An X-ray, ultrasound, CT or MRI to examine soft tissue and bone are also typically performed to diagnose and confirm gout.

[0005] Identifying monosodium urate crystals in joint fluid is a typical way to diagnose gout. Injecting a needle into the joint and removing synovial fluid from the affected joint and examining it under a microscope for uric acid crystals is typically done for gout diagnosis.

[0006] Also, while gout is caused by uric acid crystals, pseudo gout is caused by calcium pyrophosphate crystals (CPP) and CPP are often found in joint fluids along with MSU. Both these types of crystals cannot be detected and distinguished by the naked eye. Hence, a complex technique like polarized microscopy is utilized in clinical labs to distinguish and identify MSU. This technique is expensive, time consuming and also requires trained technicians to accurately identify and report gout.

[0007] Thus, what is desired is a relatively quick method and device to detect and/or diagnose gout from a sample taken from a patient.

[0008] Embodiments of the present disclosure provide devices and methods that address the above clinical needs.

SUMMARY OF THE DISCLOSURE

[0009] The present disclosure is directed to a kit and methods for using the same. The kit comprises a plate comprising at least one well, wherein the well comprises a silver nitrate and a catalyst. The method comprises providing a sample of synovial fluid to a well of a plate,

wherein the well comprises a silver nitrate and a catalyst and determining a presence of monosodium urate (MSU) crystals, wherein the presence of MSU crystals indicates that gout is detected in the sample.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The present disclosure will be better understood by reference to the following drawings, which are provided as illustrative of certain embodiments of the subject application, and not meant to limit the scope of the present disclosure.

[0011] FIG. 1 is an image of various concentrations of silver nitrate solution.

[0012] FIG. 2 is an image of various concentrations of silver nitrate films.

[0013] FIG. 3 is an image of monosodium urate (MSU) crystals in a silver nitrate solution and also in a 2% Alizarin red solution.

[0014] FIGs. 4A and 4B are illustrations of a kit configured to detect gout.

[0015] FIG. 5 is an illustration of a kit configured to detect gout.

[0016] FIGs. 6A and 6B are magnified images of a sample within the kit of FIG. 5.

[0017] FIGs. 7A-7C are illustrations of a kit configured to detect gout.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0018] In the discussion and claims herein, the term "about" indicates that the value listed may be somewhat altered, as long as the alteration does not result in nonconformance of the process or device. For example, for some elements the term "about" can refer to a variation of ±0.1%, for other elements, the term "about" can refer to a variation of ±1% or ±10%, or any point therein.

[0019] As used herein, the term "substantially", or "substantial", is equally applicable when used in a negative connotation to refer to the complete or near complete lack of an action, characteristic, property, state, structure, item, or result. For example, a surface that is "substantially" flat would either completely flat, or so nearly flat that the effect would be the same as if it were completely flat.

[0020] As used herein terms such as "a", "an" and "the" are not intended to refer to only a singular entity, but include the general class of which a specific example may be used for illustration.

[0021] As used herein, terms defined in the singular are intended to include those terms defined in the plural and vice versa.

[0022] References in the specification to "one embodiment", "certain embodiments", some embodiments" or "an embodiment", indicate that the embodiment(s) described may include a particular feature or characteristic, but every embodiment may not necessarily include the particular feature, structure, or characteristic. Moreover, such phrases are not necessarily referring to the same embodiment. Further, when a particular feature, structure, or characteristic is described in connection with an embodiment, it is submitted that it is within the knowledge of one skilled in the art to affect such feature, structure, or characteristic in connection with other embodiments whether or not explicitly described. For purposes of the description hereinafter, the terms "upper", "lower", "right", "left", "vertical", "horizontal", "top", "bottom", and derivatives thereof shall relate to the invention, as it is oriented in the drawing figures. The terms "overlying", "atop", "positioned on" or "positioned atop" means that a first element, is present on a second element, wherein intervening elements interface between the first element and the second element. The term "direct contact" or "attached to"

means that a first element, and a second element, are connected without any intermediary element at the interface of the two elements.

[0023] Reference herein to any numerical range expressly includes each numerical value (including fractional numbers and whole numbers) encompassed by that range. To illustrate, reference herein to a range of "at least 50" or "at least about 50" includes whole numbers of 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, etc., and fractional numbers 50.1, 50.2 50.3, 50.4, 50.5, 50.6, 50.7, 50.8, 50.9, etc. In a further illustration, reference herein to a range of "less than 50" or "less than about 50" includes whole numbers 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, etc., and fractional numbers 49.9, 49.8, 49.7, 49.6, 49.5, 49.4, 49.3, 49.2, 49.1, 49.0, etc.

[0024] The present disclosure includes a kit that includes a plate having at least one well, wherein the well comprises any suitable ionic silver compound, such as silver nitrate and a catalyst. This kit is configured to detect gout in a sample, such as a synovial fluid sample that has been collected from a patient. This synovial fluid sample can be collected in any suitable way, such as by a hypodermic needle.

[0025] The catalyst can be any suitable catalyst, such as formaldehyde, citric acid, glutaraldehyde, and combinations thereof. The catalyst can be in any suitable concentration, such as from about 0.001% to about 4%, or about 0.002% to about 2%, or about 0.003% to about 1%, or about 0.01% to about 0.5%, and all ranges therein. Along with the catalyst, a basic material, such as sodium bicarbonate, can also be included.

[0026] The plate of the kit can be any suitable surface and can be comprised of any suitable material, such as glass, plastic, and combinations thereof. The well includes vertical walls that rise above the surface of the plate or are sunken below the surface of the plate. The well can be any suitable shape or size and is configured to maintain a fluid within it.

[0027] Within the well, the kit includes an ionic silver compound, such as silver nitrate, at any suitable concentration, such as about 10% to about 40 %, or about 20%. As an example, 20% silver nitrate solution is about 1.34 M $AgNO_3$. Also within the well, a suitable catalyst is included. In one embodiment, the catalyst is formaldehyde, which can be at any suitable concentration, such as a concentration of about 0.002%.

[0028] Within the well the ionic silver compound, such as silver nitrate, and the catalyst can be elements of a solution that is maintained in the well, and/or, the ionic silver compound, such as silver nitrate, and the catalyst can be elements of a film that at least partially coats an internal surface of the well. The coating on the internal surface of the well can occur on a portion of or the whole bottom surface, in addition to or in replace of a portion of or the whole side wall surface of the well.

[0029] If the ionic silver compound, such as silver nitrate, and the catalyst are elements of a solution, the synovial fluid sample can be added to the solution within the well and the mixture can react.

[0030] If the ionic silver compound, such as silver nitrate, and the catalyst are elements of a film that at least partially coats an internal surface of the well, the synovial fluid sample can be added to the well to react with the film.

[0031] Optionally, as an additional component of the kit, within the well, the well can further comprise any suitable calcium detecting stain, such as alizarin red, Von Kossa stain, and combinations thereof, which can be in any suitable concentration, such as about 0.01% to about 3%, or about 0.5% or about 2%, or about 0.8% to about 1.5%, or about 2% solution of calcium detecting stain.

[0032] Optionally, as an additional component of the kit, within the well, the well can further comprise a polymerizing matrix material, such as a gelatin, an agar and combinations thereof. This polymerizing matrix material may be included in the well as an element to contact the solution of ionic silver compound and catalyst, or, the polymerizing matrix material may be included in the well as an element of the film of ionic silver compound and catalyst.

[0033] In the well, if uric acid is present in the synovial fluid sample, it reacts with the ionic silver compound, such as silver nitrate, and forms a dark or darkish color crystal, such as a monosodium urate (MSU) crystal. To aid in viewing of the MSU crystal, the kit can include and can be configured to attach to a camera to image the contents of the well after a reaction. This camera can be any suitable camera device that is capable of capturing an image, and the attachment between the camera and kit can be any suitable structural arrangement that can maintain or substantially maintain the camera's location as compared to the well.

[0034] Optionally, the camera can include a magnification system, such as one or more magnifying lenses.

[0035] In another embodiment, the kit can include a hinged cover that substantially covers an upper opening of the well. The hinged cover can include a cover bottom, which extends around an upper surface of the well, as well as a cover top. The cover top can include a magnifier, so that when the cover top is in a closed configuration, the magnifier magnifies the contents of the well.

[0036] The methods of the present disclosure can be used in conjunction with the above described kit. Methods of the present disclosure include methods of detecting gout by providing a sample of synovial fluid to the well of the plate, which comprises an ionic silver compound, such as silver nitrate, and the catalyst. The synovial fluid can be collected from any

patient in any suitable way, such as by a hypodermic needle being inserted into a joint, and the fluid therein being withdrawn into the hypodermic needle. The hypodermic needle can then be used to transport the fluid and then provide the fluid into the well.

[0037] The method then includes the determination of the presence of monosodium urate (MSU) crystals, wherein the presence of MSU crystals indicates that gout is detected in the sample. If uric acid was present in the synovial fluid, an amount of MSU crystal should be formed in the well. The MSU crystal will be dark or darkish in color as compared to the remaining fluid within the well and can be visible by the naked eye, through a magnifier or through an image (magnified or not) of the contents of the well.

[0038] The amount of time between providing the synovial fluid to the well and determining whether or not MSU crystal are present can be about 3 minutes or more, about 5 minutes or more, about 8 minutes or more, about 10 minutes or more, about 15 minutes or more, about 20 minutes or more, or more than 20 minutes.

[0039] The methods and model of the present disclosure will be better understood by reference to the following Examples, which are provided as exemplary of the disclosure and not in any way limiting.

Examples

Interaction of Uric Acid Crystals with Silver Nitrate

[0040] Uric acid interacts with silver nitrate and turns black after reducing the silver. This chemical reaction is used as the basis for detecting monosodium urate (MSU) crystals. MSU crystals were placed in glass wells of a 24-well cell culture plate and 200 µL of different concentrations of silver nitrate solution (100%, 80%, 60%, 40%, 20% and 10%) with 0.002% formaldehyde was added to each of the wells.

[0041] The culture plate was allowed to incubate at room temperature and the image of FIG. 1 was acquired. As can be seen in FIG. 1, from left to right, the concentrations of silver nitrate solution increases as indicated by the numbers above each well, from 10% to 100%. Also as can be seen in FIG. 1, 20% silver nitrate solution included maximum staining as compared to the other concentrations of silver nitrate solution.

Gout Detection Device with Pre-Coated Staining Agent

[0042] Different concentrations of silver nitrate with 0.002% formaldehyde solution were added to different wells of a well culture plate and allowed to air dry overnight. MSU crystal (1 mg/200 μL) suspension was prepared in saline and added to the wells containing the dried silver nitrate/formaldehyde film that coated inner portions of the well. FIG. 2 is an image that was acquired after addition of the suspension to the wells.

[0043] As can be seen in FIG. 2, from left to right, the concentrations of silver nitrate in the films is indicated by the numbers above each well, from 10% to 100%. Also as can be seen in FIG. 2, 20% silver nitrate solution included maximum staining as compared to the other concentrations of silver nitrate solution.

Distinguishing uric acid crystals from calcium crystals

[0044] Calcium phosphate crystals are often found to be present in joint fluids and is an indication of pseudo gout. To distinguish uric acid crystals from calcium phosphate crystals, alizarin red (2%) solution was tested on MSU crystals (also referred to herein as uric acid crystals). Silver nitrate solution turns MSU crystals black, whereas alizarin red does not interact with the MSU crystals.

[0045] In this example, alizarin red does not substantially interact with MSU crystals as the crystals remain white even after exposure of MSU crystals to alizarin red stain.

[0046] FIG. 3 is an image of a side by side comparison of MSU crystals in a silver nitrate solution and also in a 2% Alizarin red solution. On the left, the MSU crystals have interacted with the silver nitrate and are now seen as being black in color. On the right, the MSU crystals in the Alizarin red solution are not black since calcium phosphate (calcium) interacts with Alizarin red and give a deep orange to red color rather than black.

Gout detection kit

[0047] To identify MSU crystals in synovial fluid aspirated from a joint, one embodiment of a kit 1 configured to detect gout was designed one embodiment of which is shown in FIG. 4A. FIG. 4A is a side view of the kit 1. The kit 1 of FIG. 4A includes a plate 2 that comprises a well 4. In this embodiment only one well is shown, but, in other embodiments, two or more wells may be present on the plate 2. An inner side surface 3 of the well 4 can be seen in FIG. 4A.

[0048] FIG. 4B is a perspective view of the kit 1. As can be seen in FIG. 4B, the well 4 is substantially round, and in this embodiment has a diameter of 1.5 mm, but, in other embodiments, the well can be different shapes and/or larger or smaller diameters. Well 4 can be formed of any suitable material, such as plastic, glass, metal, carbon materials, and mixtures thereof. In this embodiment plate 2 is formed of a glass material, but, plate 2 can be formed of any suitable material, such as plastic, glass, metal, carbon materials, and mixtures thereof.

[0049] In the embodiment of FIG.4B, a base surface 6 of the well 4 is coated with 20% silver nitrate with 0.002% formaldehyde to form a coating 8. Coating 8 is formed in any suitable way, in this embodiment by overnight incubation and air drying of the silver nitrate and formaldehyde in the well 4. Although coating 8 is shown as discrete dots in FIG. 4, this

coating 8 did extend over the base surface 6 of the well 4. Joint fluid (about 200 uL, but can be less or more) can be added to the well 4 for detection of MSU crystals.

Gout detection kit

[0050] FIG. 5 illustrates an embodiment of kit 1, which includes a camera device 10 (in this example an iPhone® 6, but in other embodiments can be any apparatus capable of capturing images), an optional magnification system 12 (in this embodiment a Micromobile microscope (Proscope™), but in other embodiments, any suitable lens or lenses configured to magnify an image) and an optional filter 14 (in this embodiment a polarizing filter, but in other embodiments, any one or more suitable filters can be included)

[0051] In the kit of FIG. 5, MSU crystals suspension and calcium phosphate solution were added to the well 3. In this embodiment, the well 3 was pre-coated with 20% silver nitrate, 0.002% formaldehyde and 2% alizarin red. After 5 minutes, low magnification (10 X) and high magnification (100X) images were acquired with the camera device 10 of the contents of the well 5, and are shown in FIG. 6A and 6B.

[0052] FIG. 6A is an image at a magnification of 10X, FIG. 6B is an image at a magnification of 100X. The images of both FIG. 6A and 6B were acquired without the use of optional filter 14. As indicated in FIG. 6B, uric acid (MSU) crystals were formed, and are shown as being stained black.

[0053] Another embodiment of a kit 20 is shown in FIG. 7.

[0054] Kit 20 includes the plate 2 and well 4, with the well 4 being covered with a hinged cover 21. The hinged cover 21 includes a cover base 22, that extends around the upper circumference of the well 4 and has an opening therethrough (better seen in FIG. 7C), and a cover top 24. In FIG. 7A, the hinged cover 21 is shown in an open configuration.

[0055] The cover top 24 includes a magnifier 26 (better seen in FIG. 7C) that is substantially transparent or substantially translucent and is configured to magnify the contents of well 4 for observation when the hinged cover 21 is in a closed configuration (as in seen in FIGs. 7B and 7C).

[0056] Magnifier 26 can be any suitable shape and any material suitable for magnifying the contents of well 4. Some examples of the material of magnifier 26 is plastics, glasses, and combinations thereof. The shape and material of magnifier 26 can be adjusted to result in a desired magnification value, such as for example a magnification of about 60X, but, in other embodiments, the magnification can be any value between about 2X and about 100X or more.

[0057] As seen in FIG. 7B, which is a side illustration of the kit 20, hinged cover 21 can be in a closed configuration so that cover top 24 contacts or nearly contacts cover base 22.

[0058] FIG. 7C is a perspective illustration of the kit 20, with the hinged cover 21 being in a closed configuration. For illustrative purposes, the magnifier 26 is providing sufficient magnification such that MSU crystals (black dots) are visible to a human operator in the well 4, as the operator looks into the well 4 through the magnifier 26.

[0059] The described embodiments and examples of the present disclosure are intended to be illustrative rather than restrictive, and are not intended to represent every embodiment or example of the present disclosure. While the fundamental novel features of the disclosure as applied to various specific embodiments thereof have been shown, described and pointed out, it will also be understood that various omissions, substitutions and changes in the form and details of the devices illustrated and in their operation, may be made by those skilled in the art without departing from the spirit of the disclosure. For example, it is expressly intended that all combinations of those elements and/or method steps which perform substantially the same

function in substantially the same way to achieve the same results are within the scope of the disclosure. Moreover, it should be recognized that structures and/or elements and/or method steps shown and/or described in connection with any disclosed form or embodiment of the disclosure may be incorporated in any other disclosed or described or suggested form or embodiment as a general matter of design choice. Further, various modifications and variations can be made without departing from the spirit or scope of the disclosure as set forth in the following claims both literally and in equivalents recognized in law.

CLAIMS:

1. A kit comprising:

a plate comprising at least one well, wherein the well comprises a silver nitrate and a catalyst.

2. The kit of claim 1, wherein the silver nitrate and the catalyst are components of a solution within the well.

3. The kit of claim 1, wherein the silver nitrate and the catalyst are comprised in a film that at least partially coats a surface of the well.

4. The kit of claim 1, wherein the silver nitrate is in a range of concentration of about 10% to about 40%.

5. The kit of claim 1, wherein the silver nitrate is at a concentration of about 20%.

6. The kit of claim 1, wherein the catalyst is formaldehyde.

7. The kit of claim 6, wherein the formaldehyde is at a concentration of about 0.002%.

8. The kit of claim 1, wherein the kit is configured to attach to a camera.

9. The kit of claim 8, wherein the camera comprises a magnification system.

10. The kit of claim 1, wherein the well further comprises alizarin red.

11. The kit of claim 10, wherein the well further comprises a solution of about 2% alizarin red.

12. The kit of claim 1, wherein the kit further comprises a hinged cover.

13. The kit of claim 12, wherein the hinged cover comprises a cover top, wherein the cover top comprises a magnifier.

14. A method of detecting gout, the method comprising:

providing a sample of synovial fluid to a well of a plate, wherein the well comprises a silver nitrate and a catalyst;

determining a presence of monosodium urate (MSU) crystals, wherein the presence of MSU crystals indicates that gout is detected in the sample.

15. The method of claim 14, wherein the time between the providing step and the determining step is about 5 minutes.

16. The method of claim 14, wherein the silver nitrate and the catalyst are components of a solution within the well.

17. The method of claim 14, wherein the silver nitrate and the catalyst are comprised in a film that at least partially coats a surface of the well.

18. The method of claim 14, wherein the silver nitrate is at a concentration of about 20%.

19. The method of claim 14, wherein the catalyst is formaldehyde.

20. The method of claim 19, wherein the formaldehyde is at a concentration of about 0.002%.

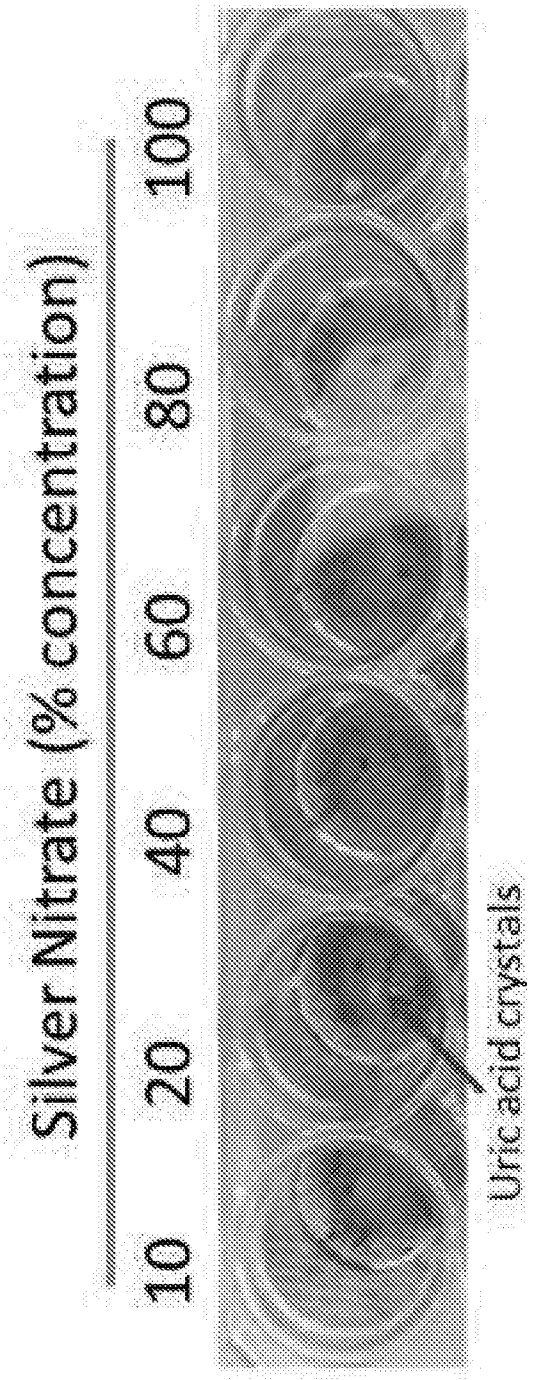
Silver Nitrate (% concentration)
10
20
40
60
80
100
Uric acid crystals

FIG. 1

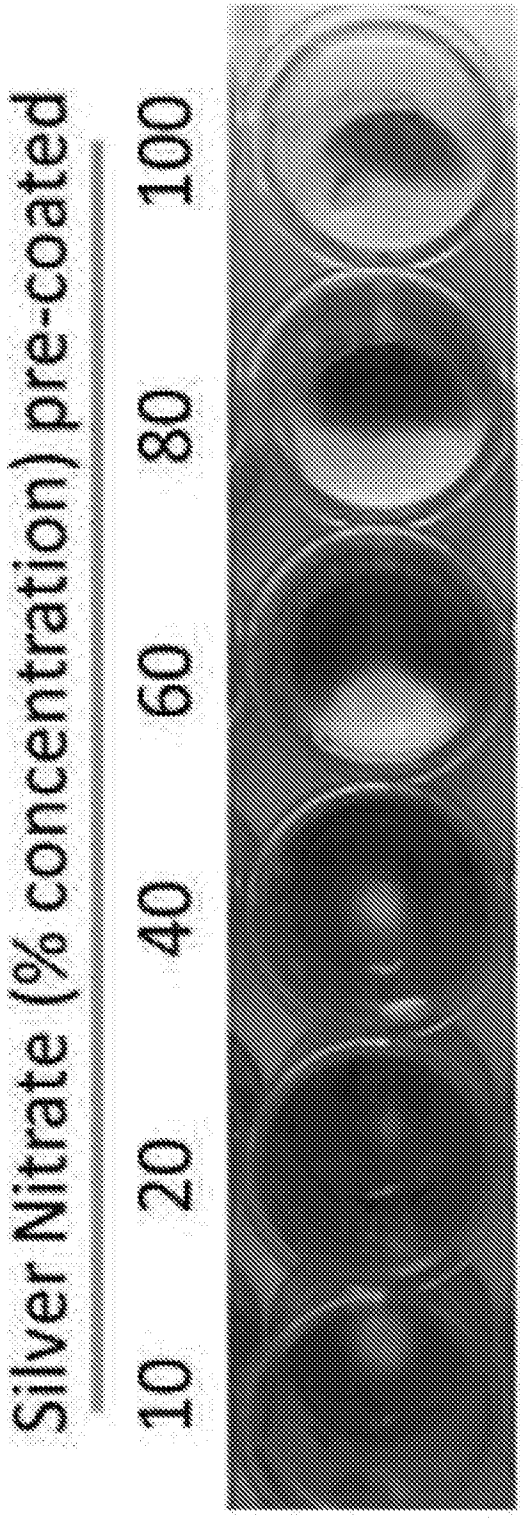

FIG. 2

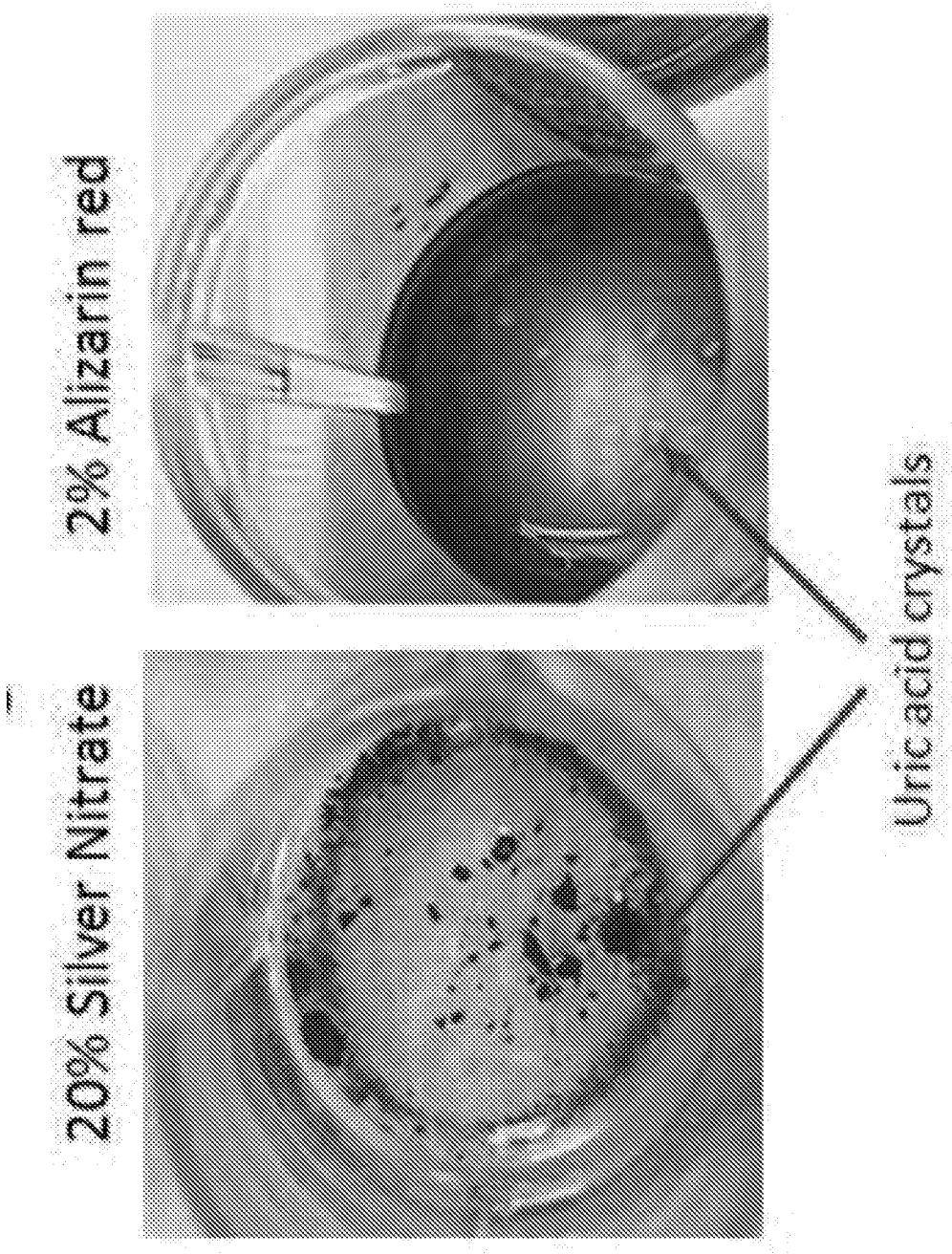

FIG. 3

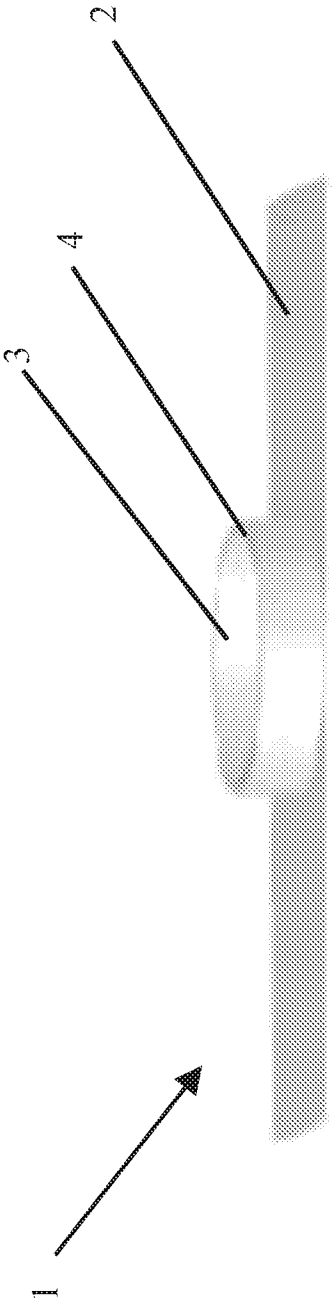

FIG. 4A

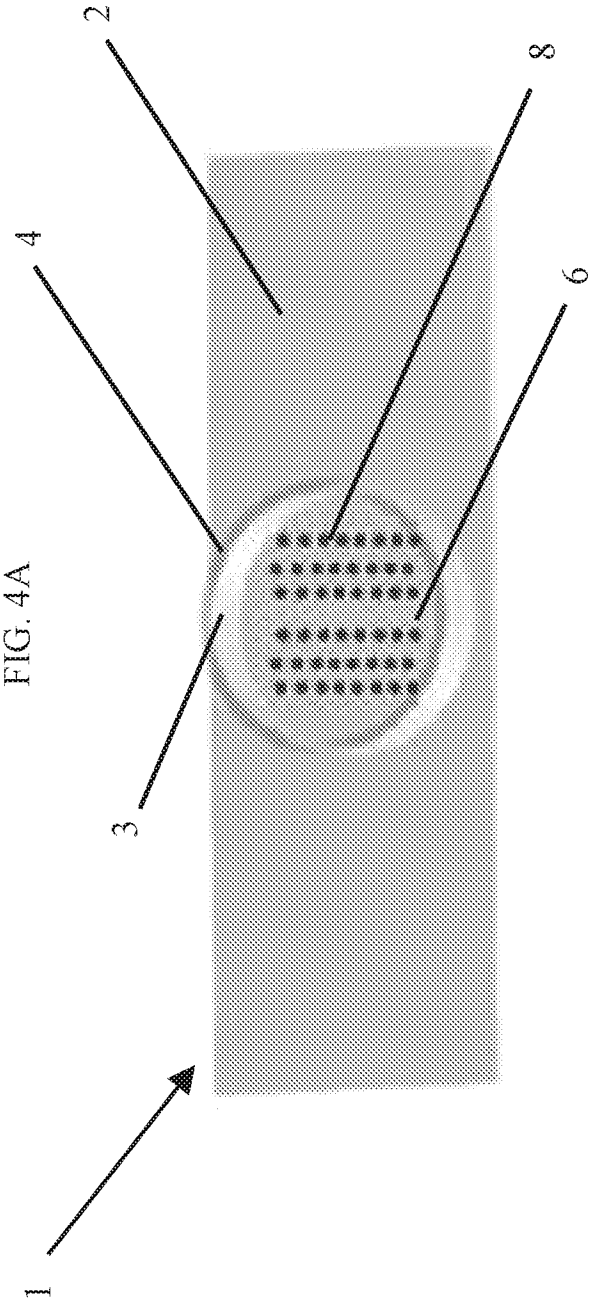

FIG. 4B

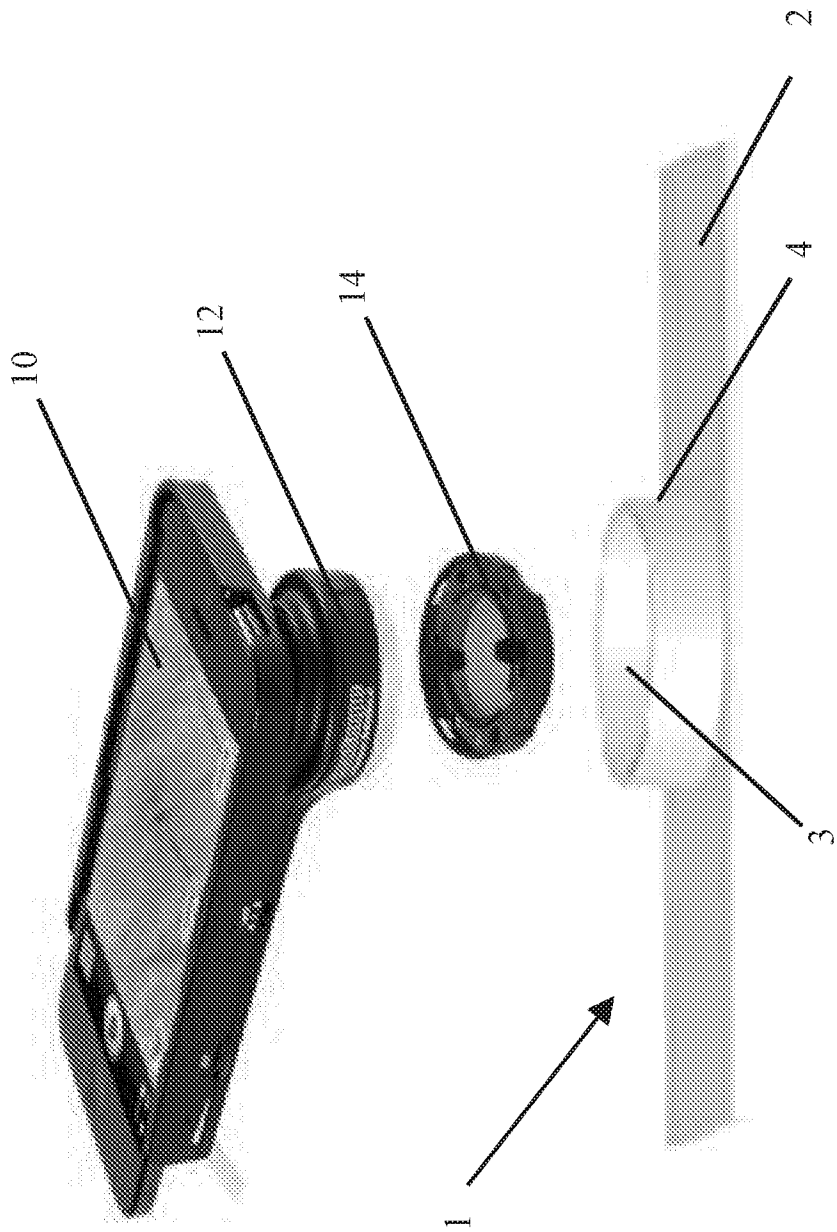

FIG. 5

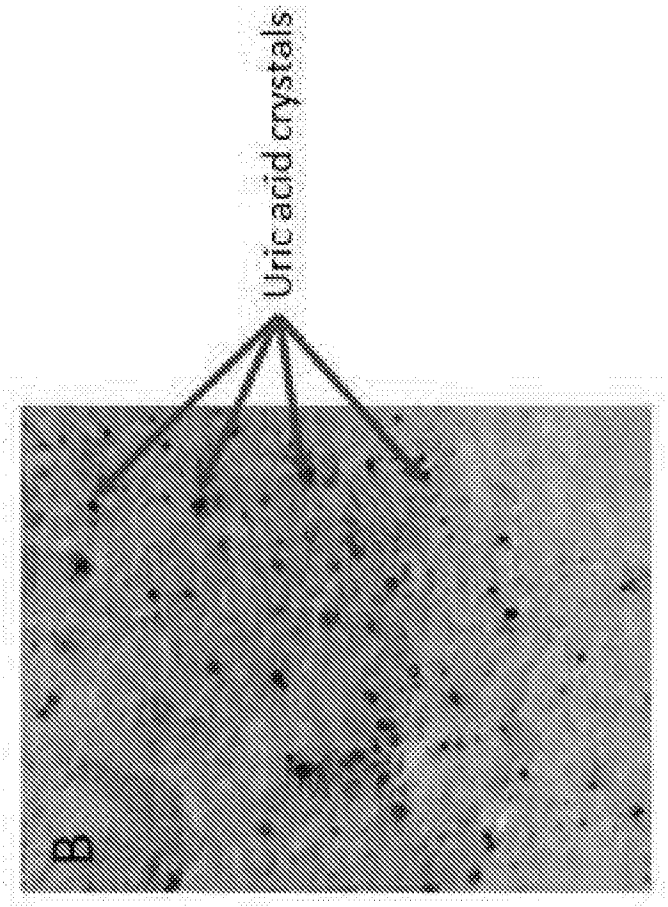

FIG. 6B

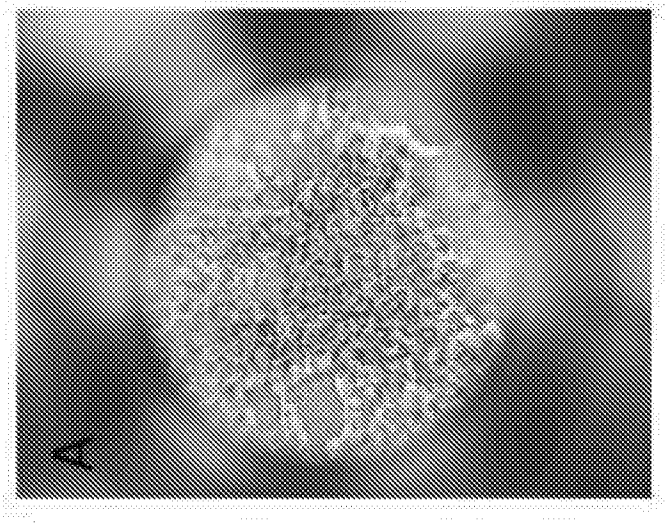

FIG. 6A

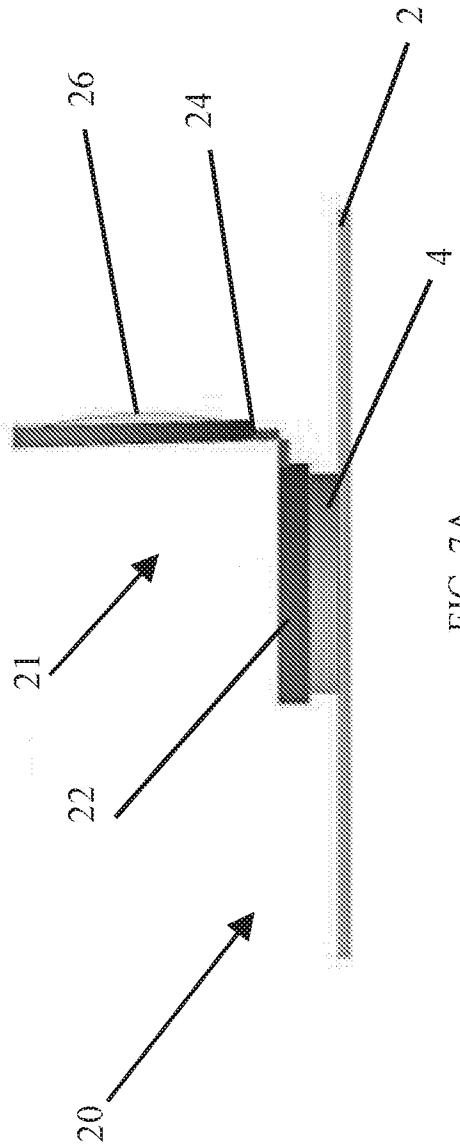

FIG. 7A

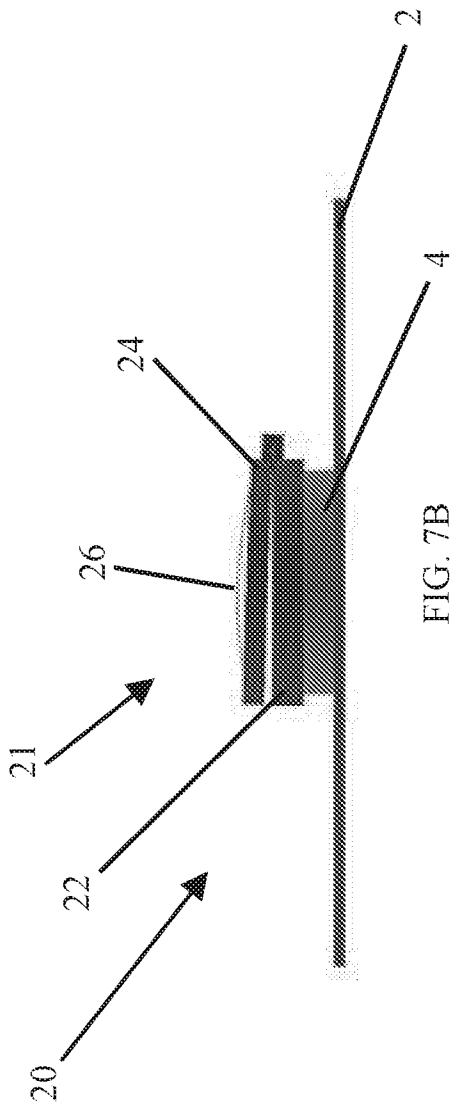

FIG. 7B

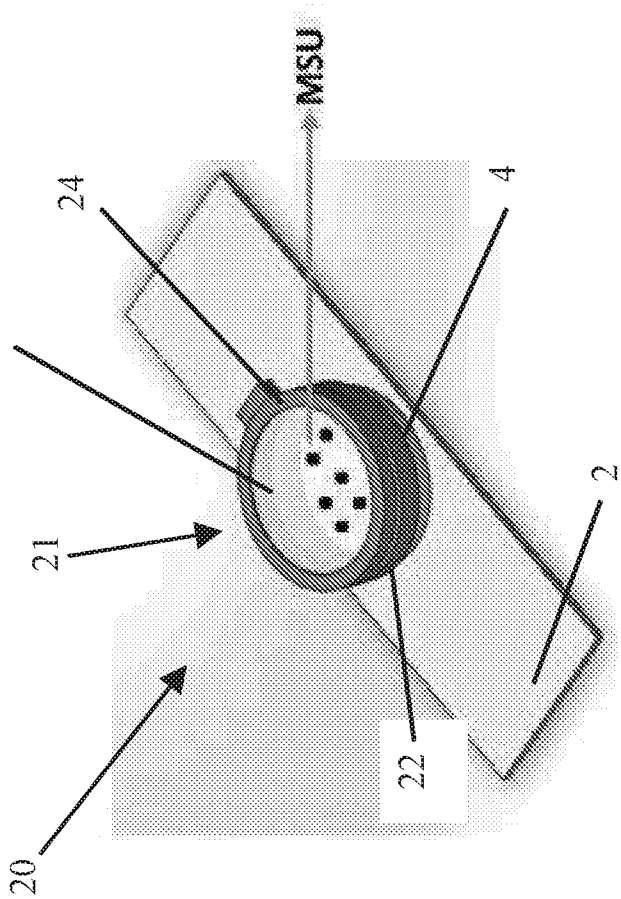

FIG. 7C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/32220

A. CLASSIFICATION OF SUBJECT MATTER
IPC - G01N 1/31, 1/30 (2018.01)
CPC - G01N 1/31, 1/30; C12M 23/00

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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	(LI, R, et al.) Synergistic Reaction of Silver Nitrate, Silver Nanoparticles, and Methylene Blue Against Bacteria. PNAS. 29 November 2016, Vol. 113, No. 48; Pages 13612-13617. www.pnas.org/cgi/doi/10.1073/pnas.1611193113; Page 13613, Left Column, Secton Paragraph; Page 13615, Right Column, Third Paragraph.	1-20
Y	WO 2004/099784 A2 (ANAMAR MEDICAL AB) 18 November 2004; Page 42, Lines 1-5; Page 44, Lines 17-28; Claim 164.	1-13
Y	(ZAMUDIO-CUEVAS, Y, et al.) Monosodium Urate Crystals Induce Oxidative Stress in Human Synoviocytes. Arthritis Research & Therapy. 2016, Vo. 18, No. 117. DOI 10.1186/s13075-016-1012-3; Abstract, Background, Methods, Conclusions Sections; Page 3 of 9, Right Column, Third Paragraph, Results Section; Page 5 of 9, Right Column, First Paragraph.	14-20
Y	(ZHANG, Y, et al.) Wide-Field Imaging of Birefringement Synovial Fluid Crystals Using Lens-Free Polarized Microscopy for Gout Diagnosis. Scientific Reports. Vol. 6:28793. 30 June 2016. DOI: 10.1038/srep28793; Abstract; Page 2, Second Paragraph; Page 11, Discussion Section, First Paragraph to Second Paragraph.	8, 9
Y	US 2008/062369 A1 (SONG, K, et al.) 13 March 2008; Abstract; Paragraphs [0003]-[0005], [0027]; Claims 1, 3	3-5, 17, 18
Y	US 2011/020170 A1 (LUNISTRA, G, et al.) 27 January 2011; Abstract	6, 7

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"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
17 July 2018 (17.07.2018)	24 AUG 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/32220

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	(FARYNA, A, et al.) Chapter 166, Joint Fluid. Clinical Methods: The History, Physical, and Laboratory Examinations, 3rd Edition. Butterworths. Boston, 1990; Page 773, Left Column, First Paragraph; Page 773, Right Column, Second Paragraph; Page 774, Left Column, Flrst Paragraph.	10, 11
Y	EP 1,967,885 A1 (OLYMPUS CORPORATION) 10 September 2008; Abstract; Paragraph [0043]; Figure 1(C)	12, 13
Y	US 6,130,023 A (COPPENS, P, et al.) 10 October 2000; Abstract; Column 11, Lines 38-46; Claim 1	7, 19, 20
Y	US 2014/329300 A1 (RARECYTE, INC.) 06 November 2014; Abstract; Paragraph [0019]	13
Y	(BOUMANS, D, et al.) The Added Value of Synovial Fluid Centrifugation for Monosodium Urate and Calcium Pyrophosphate Crystal Detection. Clin Rheumatol. 19 April 2017. DOI 10.1007/s10067-017-3633-6; Abstract; Page 3 of 7, Left Column, Element (4).	15