



(11) **EP 1 761 162 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
01.09.2010 Bulletin 2010/35

(21) Application number: **05755386.9**

(22) Date of filing: **23.06.2005**

(51) Int Cl.:
A61B 5/00 (2006.01) A61M 25/00 (2006.01)

(86) International application number:
PCT/GB2005/002456

(87) International publication number:
WO 2006/000764 (05.01.2006 Gazette 2006/01)

(54) **PH SENSOR**

PH-SENSOR

DETECTEUR DE PH

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR

(30) Priority: **24.06.2004 GB 0414222**

(43) Date of publication of application:
14.03.2007 Bulletin 2007/11

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Description

[0001] The present invention relates to a pH sensor for use in a catheter drainage system. The present invention also relates to a catheter, drainage bag or connection unit comprising the pH sensor of the present invention, methods of

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using the pH sensor and methods of making the pH sensor.

[0002] The care of many of the elderly and disabled patients undergoing long-term bladder catheterisation is complicated by the encrustation and blockage of their catheters. The problem is unpredictable and community nurses are called out at any time of the night or day to patients in discomfort with urinary retention or incontinent of urine owing to sudden blockage of the catheter. Current methods of controlling the encrustation are ineffective, and generally the replacement catheters block recurrently and the patient gains a reputation as a "blocker"[1].

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[0003] Encrustation results from infection of the catheterised urinary tract by urease producing organisms, particularly *Proteus mirabilis*. The bacterial urease generates ammonia from urea and the urine becomes alkaline (pH 8 - 9). *P. mirabilis* also colonizes the catheter surfaces and forms a biofilm. In the alkaline conditions calcium and magnesium phosphates crystallise from the urine and crystalline biofilms develop on the catheters [2]. It should be noted that commonly the urine of these patients is infected with organisms such as *Escherichia coli* which are not urease producers and their metabolism generates slightly acid urine (pH 5 - 6).

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[0004] After 2-3 weeks of catheterisation, infection is generally always present within a patient in a benign state. Antibiotics are not used as the infection will reappear when use is stopped. In long-term catheterisation patients, and as indicated above, biofilms of bacteria grow on the catheters and in some cases crystalline biofilms form, which block the catheter, this results in bladder expansion, kidney reflux, septic shock and in some cases death. Crystals can break off the biofilms and can cause side effect such as bladder stones. Additionally, in patients with spinal injuries or neurological disorders, stroke can occur. 50% of long-term patients suffer from encrustation. A UK study [3] of 467 catheterised patients being cared for in the community, recorded 507 emergency referrals related to catheter blockage over a 6 month period. Therefore there are huge costs both financially and in terms of morbidity associated with this problem and there

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is no current way of avoiding this problem.

[0005] There is a need for a simple sensor that could be incorporated into a catheter drainage system to signal that urease producing bacteria have infected the urine, thus giving an early warning signal of impending catheter encrustation and blockage.

[0006] It has been known that the detection of changes in pH of various body fluids may be desirable and a number of pH sensors have been devised. In International Patent Application WO 02/096286, a device for insertion into the urethra and that measures pH, pO₂ or pCO₂ is disclosed. This device is complicated and requires the pH sensor to be inserted into the urethra. Complicated electronic sensor equipment is also required in order to determine if there is a pH change.

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[0007] US Patent Application US 2002/0128542 discloses a pH indicator comprising a photodetector set in a glass matrix with a processing device. The device is positioned internally within an animal to determine rumen pH.

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[0008] US Patent US-A-5,596,988 discloses an indicator set into a biphasic material for measurement of blood parameters. The device is positioned within the body.

[0009] US Patent US-A-5,704,353 discloses an internally positioned sensor for measuring various parameters. The sensor is connected to optical cables so that changes in the various parameters can be monitored.

[0010] US-A-5,607,417 and US-A-5,554,147 disclose a pH sensitive matrix which releases an agent when a certain pH is reached.

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[0011] International Patent Application WO 94/10553 discloses a fibre-optic probe for measuring pH and carbon dioxide levels. The device has a complicated construction and is for insertion into a body cavity.

[0012] German Patent Application DE-A-3504527 discloses a urine collection bag with an indicator unit which can easily be used to quickly determine a pH value.

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[0013] There are a number of problems with the prior art devices. Firstly, a number of the devices require the use of complicated cables or signalling systems to enable any change in the parameter being measured to be detected. This is particularly a problem when the device is located internally within the human or animal body. A further problem is that the prior art devices do not distinguish between a sustained change in the level of the parameter being measured and a transitory change. Transitory changes in the pH of urine can occur due to a number of factors such as diet; however, a sustained increase in pH is indicative of impending catheter encrustation and blockage. A further problem with the prior art devices is that the pH indicator can leach out of the device due to the flow of urine. Such leaching will reduce the effectiveness of the pH indicator and also contaminate the urine.

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[0014] The present inventors have endeavoured to solve one or more of the problems associated with the prior art devices. In particular, the inventors have endeavoured to produce sensors from polymeric materials that have been impregnated with pH indicators. The sensors are preferably designed so that they are located in the drainage system of a catheter so that they are clearly visible to the patient/carer enabling the sensor to be continuously monitored. A change from the acid to alkaline reaction will signal infection by *P. mirabilis* or related urease producing organisms and indicate that action should be taken to avoid an acute clinical episode.

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[0015] The present invention provides a pH sensor for incorporation into a catheter drainage system at any position provided that during use it is visible, wherein the pH sensor comprises a polymer matrix comprising a chemically bound pH indicator that produces a visible signal in response to an increase in pH, wherein in use the pH indicator only responds to a sustained increase in pH.

5 **[0016]** The pH sensor can be used to detect a sustained increase in pH in its immediate vicinity. In particular, the pH sensor can be used to detect a change in the pH of a fluid (i.e. urine) coming into contact with the sensor or within a bacterial biofilm formed on the sensor, and thereby provide an indication of impending catheter encrustation and blockage. Any transitory increases in pH will not be detected and false positives will be avoided. Furthermore, by having the pH indicator chemically bound, preferably covalently bound, to the polymer matrix, it has been found that no leaching of the
10 pH indicator from the matrix occurs. The pH sensor therefore remains functional during use.

[0017] It has been found that the pH sensor of the present invention can be used to detect a change in pH of urine in a catheter system indicating that the urine is infected with urease producing bacteria (e.g., *P. mirabilis*), which is an indicator of impending catheter encrustation and blockage. It has also been found that urease producing bacteria (e.g. *P. mirabilis*) present in urine form a biofilm on the pH sensor. The formation of the biofilm on the pH sensor leads to a
15 sustained increase in pH within the biofilm which is detected by the pH sensor. Due to the fact that the urease producing bacteria form a biofilm on the sensor, the presence of such bacteria can be detected before the overall pH of the urine is increased. In particular, it has been found that the pH sensor responds to a sustained increase in pH (about pH 9) within the biofilm formed on the sensor, while the pH of the urine is at a non-indicative pH of about 6 to 7. Accordingly, it is a particular advantage of the pH sensor of the present invention that a biofilm of urease producing bacteria can form
20 on the pH sensor and that the pH sensor can detect a substantial change in pH within the biofilm, which is an early indicator of impending catheter encrustation and blockage.

[0018] The term "chemically bound" means that the pH indicator is bound within the polymer matrix by some form of chemical interaction, such as ionic interaction, hydrogen bonds, etc. Preferably the term means covalently bound.

[0019] The term "catheter drainage system" refers to a catheter and the drainage unit. The drainage unit is defined
25 as the drainage bag and drainage bag tubing for connection to the catheter.

[0020] The pH sensor of the present invention can be incorporated into the catheter drainage system at any position provided that it is visible to the patient or carer. By being visible any change in the pH indicator can be readily observed. The pH sensor may be positioned close to the inserted end of the catheter while still being visible to the patient or carer. Preferably the pH sensor is positioned in the urine drainage bag. Such positioning gives the strongest and most rapid
30 signal that encrustation is taking place on the catheter. In an alternative preferred embodiment, the pH sensor is positioned at the junction between the catheter and the drainage bag tubing. The pH sensor may be positioned at the end of the catheter that is connected to the drainage bag tubing or may be positioned in the end of the drainage bag tubing that connects to the catheter. The pH sensor may be positioned within a connection unit that connects the catheter and the tubing of the drainage bag together.

[0021] The pH sensor can be any shape provided it can be positioned into a catheter drainage system and comes
35 into contact with urine. Preferably the pH sensor is a flat disc that can be positioned within the drainage bag. Preferably the pH sensor can be inserted into a drainage bag. Alternatively, the pH sensor is an annular ring that is sized to be held within the lumen of a tube of the catheter drainage system and has a bore allowing fluid to pass through the sensor. In a further alternative embodiment, the pH sensor can be in the form of a strip which is printed onto the inner surface
40 of the catheter drainage system. The pH sensor may be printed onto the catheter drainage system using any technique, such as jet printing.

[0022] The polymer matrix can be any suitable matrix provided the pH indicator can be chemically bound and provided
45 a biofilm of urease producing bacteria can form on its surface. The polymer matrix ensures that only a sustained change in pH is measured. The rate of diffusion of ions through the polymer matrix enabling it to come into contact with the bound pH indicator is tailored so that only a sustained change in pH will trigger a change in the pH indicator. The amount of polyethylene glycol plasticiser within the polymer matrix used in the examples described herein has a direct influence on the rate of movement of ions through the matrix and controls the response rate of the sensor and thus is set at a level to ensure the desirable response. One skilled in the art can determine the required rate of ion diffusing of the matrix in order to ensure that only a sustained change in pH is measured. Preferably, the type of polymer used must have
50 suitable reactive groups to enable chemical binding of a sulphuric acid treated pH indicator. Preferred polymer matrixes include silicone rubber, polyurethane and cellulose acetate. Most preferably, the polymer matrix is cellulose acetate.

[0023] The matrix may be prepared in such a way that it allows or encourages the formation of the biofilm. For example, the matrix may be rough in texture so it is conducive to biofilm binding. The material chosen to make the matrix may have a naturally rough texture, or it may be roughened.

[0024] The pH indicator can be any agent that produces a visible signal (e.g. a colour change) in response to an
55 increase in pH that is indicative of impending catheter encrustation and blockage. Urine is normally about pH 6, but when this is raised above pH 7.6, there is a danger of catheter encrustation and blockage. Suitable pH indicators include neutral red, bromothymol blue, cresol red, phenol red, 3-(m-) nitrophenol, fluorescein and rosolic acid. When a biofilm of

Proteus mirabilis or similar urease producing organisms are formed on the pH sensor, a local pH of 8 to 10 is produced indicating there is a danger of catheter encrustation. Details of the range at which colour transition occurs for these preferred indicators as well as other indicators with lower and higher pH ranges that may be used are described in Table 1 below.

Table 1

pH indicator	pH range	colour transition
bromocresol purple	5.2 - 6.8	yellow - purple
chlorophenol red	5.4 - 6.8	yellow - red
neutral red	6.8 - 8.0	red - yellow
bromothymol blue	6.2 - 7.6	yellow - blue
cresol red	7.2 - 8.8	yellow - red
m-cresol purple	7.4 - 9.0	yellow - purple
phenol red	6.4 - 8.0	yellow - red
3 - (m -) nitrophenol	6.6 - 8.6	colourless - yellow/orange
thymol blue	8.0 - 9.6	yellow - blue
cresolphthalein	7.8 - 9.0	colourless - pink
fluorescein	7.0 - 9.0	yellow - orange
Rosolic acid	6.8 - 8.0	yellow - red
α - naphtholbenzene	9.0 - 11	yellow - blue

[0025] Preferably the pH indicator is bromothymol blue.

[0026] The pH indicator may change colour in response to an increase in pH of urine or of the bacterial biofilm that may develop on the pH sensor. Preferably the pH indicator changes colour in response to an increase in pH of the bacterial biofilm. This indicates infection by the urease producing bacterium *Proteus mirabilis* and impending catheter blockage by encrustation.

[0027] The pH indicator can be chemically bound to the matrix using a technique that retains the functionality of the pH indicator. A preferred way of chemically bonding the pH indicator to the matrix is to first react to sulphuric acid ultimately leading to reactive vinylsulfonyl groups which can bind to hydrolysed cellulose acetate. Such coupling is a standard technique well known to those skilled in the art.

[0028] The pH sensor preferably comprises between 1 and 5% w/v pH indicator.

[0029] The term "sustained increase in pH" as used herein means that an increased pH level is maintained for more than 6 hours, preferably for more than 9 hours and most preferably for more than 12 hours. If an increased pH level is maintained for more than 6, 9 or 12 hours, it is more likely that the change in pH is due to urease-producing bacteria causing encrustation of the catheter rather than any other factor (e.g. diet).

[0030] The pH sensor of the present invention may, depending on the matrix used, comprise a matrix stabiliser to improve the retention of the pH indicator. It is advantageous to retain the pH indicator so that the effectiveness of the pH indicator is maintained during use. Furthermore, leaching of the pH indicator from the pH sensor will contaminate the fluid passing over the sensor. Various matrix stabilisers can be used, such as Scotchlite and quaternary ammonium compounds such as hexadecyltributyl ammonium bromide. Quaternary ammonium compounds can be used as surface-active agents and are strongly adsorbed by many substances. They produce positively charged ions in solution and help retention of pH indicators when deprotonation has occurred.

[0031] In a particularly preferred embodiment, the pH sensor of the present invention comprises cellulose acetate as the matrix and bromothymol blue as the pH indicator. In addition polyethylene glycol may be incorporated as a plasticizer which adds flexibility to the matrix and also influences the rate of response of the sensor to an increase in pH. It has been found that this combination is particularly good at detecting a sustained increase in pH that is indicative of impending catheter encrustation and blockage.

[0032] The pH sensor of the present invention may be provided in combination with a reference material to assist one with determining whether the visual signal (e.g. colour change) indicating that there is a sustained increase in pH has been obtained. The reference material is preferably fused to the pH sensor. For example, when the visual signal is a colour change, the reference material may be the colour of the pH sensor before and/or after a sustained increase in pH. Preferably, the reference material is the colour of the pH sensor after a sustained increase in pH. If the colour of the pH sensor and the reference material are identical, then there has been a sustained increase in pH. When the pH sensor is applied as a printed strip, it may be bordered by reference strips. The reference strips may be printed on the inner surface or outer surface of the catheter drainage system.

[0033] The present invention also provides a catheter comprising the pH sensor of the present invention. The pH sensor is positioned so that it can be seen by the patient or carer when the catheter is in use. It is preferred that the pH sensor is positioned close to the end of the catheter to be inserted but will still be visible to the patient or carer once the catheter has been inserted. In a particularly preferred embodiment, the pH sensor is positioned at the end of the catheter that in use is connected to the drainage bag tubing. The present invention also provides a drainage unit comprising the pH sensor of the present invention. The pH sensor is positioned so that it can be seen by the patient or carer when the drainage unit is in use. In a particularly preferred embodiment, the pH sensor is positioned at the end of the drainage bag tubing that in use is connected to the catheter.

[0034] The present invention also provides a drainage bag comprising the pH sensor of the present invention.

[0035] The present invention also provides a connection unit comprising the pH sensor of the present invention, wherein the connection unit can be inserted between the drainage unit and the catheter. The connection unit has the advantage that it can be used with existing catheters and drainage units, is easier and cheaper to manufacture and can easily be replaced without having to replace the catheter or drainage unit.

[0036] The present invention also provides the use of the pH sensor of the present invention for predicting impending catheter encrustation and blockage comprising positioning the pH sensor in the flow of urine from a catheter and monitoring for a change in the pH sensor indicating a sustained increase in pH. By predicting impending catheter encrustation and blockage, remedial action can be taken, such as replacing the catheter, to ensure that the catheter does not become blocked. As indicated above, the pH sensor can be positioned within the catheter drainage system at any position provided that it is visible to the patient or carer. In a particularly preferred embodiment, the pH sensor is positioned in the drainage bag. Alternatively, the pH sensor may be positioned within a connection unit that connects the catheter and the drainage unit together.

[0037] The present invention also provides a method of the making the pH sensor of the present invention comprising covalently linking the pH indicator to the polymer matrix and then curing the derived composition to form the pH sensor. Preferably, the polymer matrix comprises polyethylene glycol to increase the flexibility of the material and to optimise the response rate of the sensor to an increase in pH.

[0038] The specific steps of making the pH sensor will vary depending on the exact pH indicator and polymer matrix used. However, those skilled in the art are aware of suitable techniques for making the pH sensor of the present invention.

[0039] The present invention is now described by way of example only with reference to the following figures.

Figure 1 shows schematically a laboratory model of the catheterised bladder;

Figure 2 shows the reaction of the Bromothymol blue/cellulose acetate polymer to 6 h immersion in buffers at pHs ranging from 5.0 to 10.0;

Figure 3 shows the elution of bromothymol blue from the sensor in flows of buffer at pHs 6.2 and 8.0;

Figure 4 shows the signal from the pH sensors in bladder models infected with *P. mirabilis*; and

Figure 5 shows scanning electron micrographs of the sensor after 47 h in the *P. mirabilis* infected model (Figure 4A is at low magnification (12x) and Figure 4B is at high magnification (6469x)).

EXAMPLES

[0040] To prove the basic concept of the sensor the inventors need to:

1. Demonstrate that the pH indicator in the polymer matrix responds to pH changes at the sensor surface.
2. Demonstrate that the indicator does not leach out of the polymer. That it is stable in the polymer matrix and able to signal the surface pH in a flowing system, for the normal life time of a drainage bag (1 week).
3. Establish that at its preferred site in the drainage bag and the alternative site at the junction of the catheter and the drainage bag tubing, the sensor will signal crystalline biofilm formation on the eye-hole/inflation balloon region, the site at which catheter blockage usually occurs. The drainage bag and the junction of the catheter and the drainage tube have been identified as suitable locations for the sensor because of the requirement for visibility and because it could be fitted into existing drainage systems without necessitating changes to the manufacturing procedures for the catheter.
4. Establish that the sensor signals catheter encrustation well before the catheter blocks.

5. Ensure that any transient changes in the pH of the bulk urine which could result from changes in diet, do not produce false positive signals or confound the response of the sensor to the pH generated by the surface colonising crystalline biofilm.

6. Demonstrate that the sensor does not react when non-urease producing organisms are responsible for urinary infections, but remains capable of signalling any subsequent colonization of the catheterised urinary tract by *P. mirabilis*.

[0041] The ability of a pH sensors according to the present invention to meet these specifications has been tested in experiments performed on a laboratory model of the catheterised bladder. The model and its operation has been described in detail previously [4].

METHODS AND MATERIALS

Chemically Bonding Indicators via Sulphuric Acid Treatment

[0042] The method for covalently binding the indicator involved the initial treatment of the indicator in concentrated sulphuric acid. The sulphuric acid converts the hydroethylsulfo groups of the dye into sulfo esters and when the sulphuric acid is eliminated reactive vinylsulfonyl groups are formed. These reactive groups can react with the hydrolysed cellulose (cell-OH) thus chemically binding to the polymeric matrix (see below).

Schematic of the chemical structure of indicator-cellulose conjugate

Example 1 - Sensor Formulation

[0043]

- Bromothymol blue (BTB)
- Cellulose acetate beads (CA)
- PEG 5000
- Concentrated sulphuric acid
- Acetone

[0044] Cellulose acetate beads are dissolved in acetone (30% cellulose acetate: 70% acetone).

[0045] A mixture of BTB and sulphuric acid is prepared (20% BTB w/v) and left for at least 1 hour. The sulphuric acid converts the hydroethylsulfo groups on the BTB into sulfo esters, which can then bind the BTB to hydrolysed cellulose acetate.

[0046] A portion of the cellulose acetate that has previously been dissolved in acetone is then mixed with sulphuric acid (10% sulphuric acid) in order to hydrolyse it and is then left for no more than 30 min before use (due to discoloration).

[0047] The constituents of the sensor (shown below) are then mixed together vigorously on a glass slab:

Dissolved cellulose acetate (80%)

Sulphuric acid/BTB mixture (1-5% - depending on the concentration of the sensor) Sulphuric acid/cellulose acetate mixture (10%)

PEG 5000 (5%)

[0048] This mixture is then spread evenly over the glass slab and left for 30 min to allow the acetone to evaporate. The sensor is then placed in distilled water overnight to wash away traces of acid.

[0049] The sensors are then stored in the fridge prior to use.

The Bladder Model

[0050] In essence, the model consists of a glass chamber (1) (200 ml) maintained at 37° C by a water jacket (3) (Figure 1). The Model is sterilized by autoclaving and then a catheter (size #14) (5) inserted aseptically into the vessel through sections of silicone tubing (7) attached to a glass outlet at the base. The catheter balloon was inflated with 10 ml of water, securing the catheter in position and sealing the outlet from the "bladder". The catheters was then attached to a drainage tube (11) and reservoir bag. One possible position of the sensor at the catheter-drainage bag tube junction is shown in Figure 1. Sterile artificial urine was supplied to the bladder via a peristaltic pump. In this way a residual volume

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of urine (30 ml) collects in the bladder below the level of the catheter eye-hole. As urine continues to be supplied to the model, the overflow drains through the catheter to the collecting bag.

[0051] The test organism for these experiments was *P. mirabilis* B2 a clinical isolate from an encrusted catheter. The inoculum for the bladder (1 ml of a young log phase batch culture in the urine medium) was added to 20 ml of residual medium in the bladder and the culture allowed to incubate in the vessel for 1 h to establish itself before the supply of urine at a rate of 0.5 ml/min was switched on. Under these circumstances stable bladder populations of 10^7 - 10^8 cfu/ml develop in the urine in the bladder chamber.

[0052] At the end of the experimental period the supply of urine to the bladder was turned off, the balloon deflated and the catheter removed through the base of the model. The formation of the biofilm and encrustation on the surfaces of the catheters was visualized by scanning electron microscopy.

RESULTS

[0053] Preliminary experiments with a range of polymer/indicator formulations suggested that the material produced by the covalent bonding of bromothymol blue to cellulose acetate was likely to be suitable for use in the manufacture of the sensor. The response of this material to soaking in a range of pH buffer solutions for 6 h is presented in Figure 2. It can be seen that the colour transition from yellow to blue occurs over the range 6.6 to 8.0.

[0054] Prototype sensors composed of strips of the bromothymol blue/cellulose acetate polymer were produced, and inserted into drainage bags. They were also formed into rings and inserted into the catheter drainage system at the catheter-drainage bag tube junction.

Performance of the Bromothymol blue/cellulose acetate sensor in bladder models under flow regimes of buffer solutions

[0055] Initially the sensor located at the junction of the catheter and drainage tube was exposed to a flow of buffer (pH 8.0) at 0.5 ml/min for 48h in the model. A strong visible signal was detected 22 h after exposure to the buffer.

[0056] Spectrophotometric methods revealed essentially no elution of the indicator from the polymer over the 48 h.

[0057] The sensor was also exposed to flows of pH 6.2 buffer for 4 days and then pH 8.0 buffer for a further 4 days. In this case a visible signal was observed 32 h after exposure to the flow of alkaline solution. The data presented in Figure 3 demonstrate that very little (only 7% of the BTB present in the sensor) eluted from the device on exposure to the flows of buffer for 8 days.

Performance of the Bromothymol blue/cellulose acetate sensor in bladder models infected with *Proteus mirabilis*

[0058] Bladder models were fitted with catheter drainage systems containing prototype sensors at the catheter/drainage tube junction and in the drainage bag. The models were supplied with artificial urine and inoculated with *Proteus mirabilis*. The times at which the sensors produced strong visible signals and the times the catheters took to block were recorded. The results of four replicated experiments are summarised in Table 2 and illustrated in Figure 4. It is clear that the signal from the sensor in the bag was stronger and appeared more rapidly and thus gave earlier warning of catheter blockage. The mean time from the appearance of the signal to the blockage of the catheter being 33 h for the sensor in the catheter/drainage tube junction and 43 h for the sensor in the drainage bag.

TABLE 2

The times sensors took to give signals in bladder models infected with <i>Proteus mirabilis</i>			
	Appearance of signal	Appearance of signal	Time at which catheter
Experiment	from sensor located at	from sensor located in	blockage occurred
Number	the catheter-drainage	the drainage bag	(h)
	tube junction (h)	(h)	
1	20	12	64
2	26	16	51
3	21	10	49
4	22	11	57
Mean	22.25	12.25	55.25

(continued)

The times sensors took to give signals in bladder models infected with <i>Proteus mirabilis</i>			
	Appearance of signal	Appearance of signal	Time at which catheter
Experiment	from sensor located at	from sensor located in	blockage occurred
Number	the catheter-drainage	the drainage bag	(h)
	tube junction (h)	(h)	
Mean time (h)			
from signal	33	43	
to catheter			
blockage			

[0059] Statistical analysis (t-test) was performed between the data for the means times the signals appeared on the sensor located at the catheter-bag junction and on the sensor in the drainage bag. The t-test produced a significant P value of 0.00076.

[0060] The sensors were removed from the models at the end of the experiment and examined by electron microscopy. The micrographs (Figure 5) show the presence of bacterial biofilm colonising the sensor. This result is important because it shows that while the biofilm forms most extensively and blocks the catheter at or just below the eye-holes, it also forms on the surface of sensors placed at the catheter/drainage tube junction and in the urine bag, sites that are easily visible to the patient or carer.

Performance of the Bromothymol blue/cellulose acetate sensor in bladder models infected with *Escherichia coli* and *Proteus mirabilis*

[0061] Experiments were performed to test whether the sensors in models infected with organisms that do not generate alkaline urine (eg *E. coli*) are capable of responding to subsequent infection with *P. mirabilis*. Two control models were infected with either *E. coli* or *P. mirabilis*. A third model was infected with *E. coli*, incubated for 48h and then super-infected with *P. mirabilis*. The control model infected with *P. mirabilis* produced a clear signal at 15 h and the catheter blocked at 59 h. The model infected with *E. coli* alone drained freely for the 120 h of the experimental period and no signal was given by the sensor. In the third model the blue signal became visible at 75 h (27h after the introduction of the *P. mirabilis*) and the catheter blocked at 117h.

CONCLUSIONS

[0062]

1. The BromoThymol Blue/Cellulose Acetate polymer responds clearly to changes in pH over the range 6.6 to 8.0.
2. Sensors prepared from the BromoThymol Blue/Cellulose Acetate polymer take time to respond to the surface pH. They took 20-30 h to respond to the pH of flows of buffer solutions and 12 h to respond to urine infected with *P. mirabilis*. These data indicate that the sensors will not respond to transient changes in the pH of the fluid flowing over them.
3. The BromoThymol Blue does not elute in any quantity from the sensor under flowing conditions. In tests over 8 days only 7% of the indicator in the sensor eluted into buffer solutions.
4. At its preferred location in the drainage bag, the sensor is capable of signalling biofilm formation at the catheter eye-hole. The signal also becomes visible well before (approximately 43 h in infected bladder models) the catheters block.
5. The sensor does not respond when the catheterised urinary tract is infected with organisms which do not produce urease (eg *E. coli*). If *P. mirabilis* subsequently infects such a catheterised tract however, the sensor is able to respond and signal that conditions required for encrustation have been established.

CLINICAL TRIAL OF THE SENSOR

[0063] Twenty patients undergoing long-term indwelling bladder catheterisation were recruited for the study. Some patients had no encrustation problems others were experiencing frequent catheter blockage. Sterile sensors produced by the method indicated above, were aseptically introduced into newly fitted urine bags. At the time of catheter change, the new catheters were attached to sterile drainage bags fitted with the pH sensors. The bags were changed at the usual weekly intervals. Urine samples were taken at the end of each week for bacteriological analysis and pH measurement. Each patient was followed until their catheter was removed on schedule or because it had blocked. Catheters were examined for encrustation by digital photography and scanning electron microscopy. Photographs were also taken of the sensor after exposure to the urine for 2 and 7 days. The colours registered by the sensor at various pHs in patient's urine were rather darker than in the artificial urine that had been used in the laboratory experiments. The positive signal from the sensor was recognized as a dark blue/black colour. A summary of the results is presented in Table 3.

Table 3. Summary of results from clinical study on the sensor

Patient Group	Number of patients	Number of cases where sensor signalled
Infected with <i>P. mirabilis</i>	15	15
Encrustation found on catheters	15	15
Not infected with <i>P. mirabilis</i>	5	0
Catheters showed no signs of encrustation	5	0
Catheters were removed due to blockage	12	12
Catheters were removed on schedule	8	3

[0064] The sensor signalled all 15 of the cases in which *P. mirabilis* was present in the urine and catheter encrustation was observed. In the 12 cases in which unscheduled removal of the catheter due to blockage was reported, the mean time between the signal (as observed by the visiting nurse) and blockage was 1.8 weeks. There were three cases where the sensor had turned blue/black and yet the catheters drained freely for the scheduled 12 weeks. Examination of each of these catheters, however, revealed the presence of encrustation. In one case the patient acquired a *P. mirabilis* infection in week 5 of the study (during a period of respite care in hospital). Enquiries revealed that subsequent catheters blocked regularly at 3 to 4 week intervals. In the second case the patient became infected with *P. mirabilis* from week 4 onwards. This patient was a young male who made a point of having a high fluid intake. This is an extremely interesting observation in view of laboratory studies showing that a high fluid intake slows the rate of catheter encrustation. In the third of these cases *P. mirabilis* was recovered from the patients urine throughout the 12 weeks and the sensor produced a signal from week 1. Electron micrographs of this catheter show that although it had not blocked, extensive encrustation had taken place.

[0065] The results of the pH measurements on the urine revealed many examples when the sensor was dark/blue black in colour yet the urine was acid. Electron microscopy on sensors removed from patients bags showed them to be covered with crystalline biofilm. These observations indicate that the sensor is responding to the pH of the *P. mirabilis* surface biofilm rather than the pH of urine.

CONCLUSIONS

[0066]

1. The clinical study confirmed that the change in the sensor from golden yellow to dark blue/black indicated that the patient was infected with *P. mirabilis* and that catheter encrustation was occurring.
2. The sensor recorded the pH of the biofilm on its surface rather than the pH of the urine in the bag.
3. In those patients whose catheters blocked the sensor signalled encrustation at a mean time of 1.8 weeks before blockage occurred.

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[0067]

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3. Kohler-Ockmore J, Feneley RJC (1996) Long-term catheterisation of the bladder: prevalence and morbidity. *British Journal of Urology*, 77: 347-351.

10 4. Stickler DJ, Morris NS, Winters C, (1999) Simple physical model to study formation and physiology of biofilms on urethral catheters. *Methods in Enzymology* 310: 494.

Claims

15 1. A pH sensor for incorporation into a catheter drainage system, at any position provided that during use it is visible, wherein the pH sensor comprises a polymer matrix comprising a chemically bound pH indicator, wherein in use the pH indicator only responds to a sustained increase in pH, **characterised in that** the pH indicator produces a visible signal in response to said increase in pH.

20 2. The pH sensor according to claim 1 that is formed as a disc for insertion into a drainage bag of a catheter drainage system.

25 3. The pH sensor according to claim 1, that is formed as an annular ring having a bore allowing fluid to pass through the sensor.

4. The pH sensor according to any one of the preceding claims, wherein the polymer matrix is polyurethane or cellulose acetate.

30 5. The pH sensor according to any one of the preceding claims, wherein the pH indicator changes colour in response to an increase in pH of a bacterial biofilm that develops on the sensor surface.

35 6. The pH sensor according to any one of the preceding claims, wherein the pH indicator changes colour in response to an increase in pH from pH 6 to pH 7.6 or above.

7. The pH sensor according to any one of the preceding claims, wherein the pH indicator is selected from bromocresol purple, chlorophenol red, neutral red, bromothymol blue, cresol red, m-cresol red, m-cresol purple, phenol red, 3-(m-) nitrophenol, thymol blue, cresolphthalein, fluorescein, Rosolic acid and α -naphtholbenzene.

40 8. The pH sensor according to any one of the preceding claims, wherein the pH indicator is neutral red, bromothymol blue, cresol red, phenol red, 3-(m-) nitrophenol, fluorescein and rosolic acid.

45 9. The pH sensor according to any one of the preceding claims, wherein in use the pH indicator responds to an increase in the pH, when the increased pH level is maintained for more than 6 hours.

10. The pH sensor according to any one of the preceding claims, wherein in use the pH indicator responds to an increase in the pH, when the increased pH level is maintained for more than 9 hours.

50 11. The pH sensor according to any one of the preceding claims, wherein in use the pH indicator responds to an increase in the pH, when the increased pH level is maintained for more than 12 hours.

12. The pH sensor according to claim 1, which additionally comprises a matrix stabiliser.

55 13. The pH sensor according to claim 12, wherein the matrix stabiliser is a quaternary ammonium compound.

14. The pH sensor according to claim 1, wherein the polymer matrix is cellulose acetate and the pH indicator is bromothymol blue.

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15. The pH sensor according to any one of the preceding claims, which is provided with a reference material to assist in determining when the pH indicator has responded to a sustained increase in pH.
16. A catheter comprising a pH sensor according to any one of the preceding claims.
17. A drainage bag comprising a pH sensor according to any one of claims 1 to 14.
18. The catheter according to claim 16, wherein the pH sensor is positioned at the end of the catheter that in use is connected to a drainage unit.
19. A drainage unit comprising a pH sensor according to any one of claims 1 to 14.
20. The drainage unit according to claim 19, wherein the drainage unit comprises a drainage bag and drainage bag tubing, and the pH sensor is positioned at the end of the drainage bag tubing that in use is connected to the catheter.
21. A connection unit comprising the pH sensor according to any one of claims 1 to 14, wherein the connection unit can be inserted between a drainage unit and a catheter.
22. Use of the pH sensor according to any one of claims 1 to 14 for predicting impending catheter encrustation and blockage comprising positioning the pH sensor in the flow of urine from a catheter and monitoring for a change in the pH sensor indicating a sustained increase in pH.
23. A method of making a pH sensor according to any one of claims 1 to 14, comprising covalently linking the pH indicator to the polymer matrix and then curing the derived composition to form the pH sensor.
24. The method of claim 23, wherein the polymer matrix comprises polyethylene glycol.

Patentansprüche

1. pH-Sensor zum Einfügen in ein Katheter-Drainage-System an irgendeiner Stelle, so dass er während der Verwendung sichtbar ist, wobei der pH-Sensor eine Polymermatrix aufweist, die einen chemisch gebundenen pH-Indikator aufweist, wobei der pH-Indikator während der Verwendung nur auf einen anhaltenden pH-Anstieg anspricht, **dadurch gekennzeichnet, dass** der pH-Indikator ein sichtbares Signal als Antwort auf den pH-Anstieg erzeugt.
2. pH-Sensor gemäß Anspruch 1, der wie eine Scheibe für das Einsetzen in einen Drainagebeutel eines Katheter-Drainage-System geformt ist.
3. pH-Sensor gemäß Anspruch 1, der wie ein Ring mit kreisförmigem Querschnitt geformt ist, der eine Bohrung aufweist, die erlaubt, dass ein Fluid durch den Sensor fließt.
4. pH-Sensor gemäß einem der vorangegangenen Ansprüche, wobei die Polymermatrix Polyurethan oder Celluloseacetat ist.
5. pH-Sensor gemäß einem der vorangegangenen Ansprüche, wobei der pH-Indikator als Antwort auf einen pH-Anstieg eines bakteriellen Biofilms, der sich auf der Sensoroberfläche entwickelt, die Farbe ändert.
6. pH-Sensor gemäß einem der vorangegangenen Ansprüche, wobei der pH-Indikator als Antwort auf einen pH-Anstieg von pH 6 zu pH 7,6 oder darüber die Farbe ändert.
7. pH-Sensor gemäß einem der vorangegangenen Ansprüche, wobei der pH-Indikator ausgewählt ist aus Bromkresolviolett, Chlorphenolrot, Neutralrot, Bromthymolblau, Kresolrot, m-Kresolrot, m-Kresolviolett, Phenolrot, 3-(m-) Nitrophenol, Thymolblau, Kresolphthalein, Fluorescein, Rosolsäure und α -Naphtholbenzein.
8. pH-Sensor gemäß einem der vorangegangenen Ansprüche, wobei der pH-Indikator Neutralrot, Bromthymolblau, Kresolrot, Phenolrot, 3-(m-) Nitrophenol, Fluorescein oder Rosolsäure ist.
9. pH-Sensor gemäß einem der vorangegangenen Ansprüche, wobei der pH-Indikator während der Verwendung auf

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einen pH-Anstieg anspricht, wenn das angestiegene pH-Niveau länger als 6 Stunden andauert.

5 10. pH-Sensor gemäß einem der vorangegangenen Ansprüche, wobei der pH-Indikator während der Verwendung auf einen pH-Anstieg anspricht, wenn das angestiegene pH-Niveau länger als 9 Stunden andauert.

11. pH-Sensor gemäß einem der vorangegangenen Ansprüche, wobei der pH-Indikator während der Verwendung auf einen pH-Anstieg anspricht, wenn das angestiegene pH-Niveau länger als 12 Stunden andauert.

10 12. pH-Sensor gemäß Anspruch 1, der zusätzlich einen Matrixstabilisator aufweist.

13. pH-Sensor gemäß Anspruch 12, wobei der Matrixstabilisator eine quartäre Ammoniumverbindung ist.

14. pH Sensor gemäß Anspruch 1, wobei die Polymermatrix Celluloseacetat und der pH-Indikator Bromthymolblau ist.

15 15. pH-Sensor gemäß einem der vorangegangenen Ansprüche, der mit einem Referenzmaterial ausgestattet ist, um beim Feststellen wann der pH-Indikator auf den anhaltenden pH-Anstieg angesprochen hat, zu helfen.

16. Katheter, der einen pH-Sensor gemäß einem der vorangegangenen Ansprüche aufweist.

20 17. Drainagebeutel, der einen pH-Sensor gemäß einem der Ansprüche 1 bis 14 aufweist.

18. Katheter gemäß Anspruch 16, wobei der pH-Sensor am Ende des Katheters angeordnet ist, der während der Verwendung mit einer Drainageeinheit verbunden ist.

25 19. Drainageeinheit, die einen pH-Sensor gemäß einem der Ansprüche 1 bis 14 aufweist.

30 20. Drainageeinheit gemäß Anspruch 19, wobei die Drainageeinheit einen Drainagebeutel und einen Drainagebeutel-schlauch aufweist, und der pH-Sensor am Ende des Drainagebeutel-schlauchs angeordnet ist, der während der Verwendung mit dem Katheter verbunden ist.

21. Verbindungseinheit, die einen pH-Sensor gemäß einem der Ansprüche 1 bis 14 aufweist, wobei die Verbindungseinheit zwischen eine Drainageeinheit und einen Katheter eingesetzt werden kann.

35 22. Verwendung eines pH-Sensors gemäß einem der Ansprüche 1 bis 14 zum Vorhersagen drohender Katheterverkrustung und -verstopfung, die das Anordnen des pH-Sensors in den Urinabfluss eines Katheters und das Überwachen einer Änderung im pH-Sensor aufweist, die einen anhaltenden pH-Anstieg anzeigt.

40 23. Verfahren zur Herstellung eines pH-Sensors gemäß einem der Ansprüche 1 bis 14, das kovalentes Binden des pH-Indikators an die Polymermatrix und anschließendes Aushärten der erhaltenen Zusammensetzung, um den pH-Sensor zu bilden, aufweist.

24. Verfahren gemäß Anspruch 23, wobei die Polymermatrix Polyethylenglykol aufweist.

45 **Revendications**

50 1. Sonde de pH pour incorporation à un système de drainage par cathéter, à n'importe quelle position à condition qu'elle soit visible au cours de l'utilisation, la sonde de pH comprenant une matrice polymère comprenant un indicateur de pH lié de manière chimique, dans laquelle, en cours d'utilisation, l'indicateur de pH ne répond qu'à une augmentation de pH soutenue, **caractérisée en ce que** l'indicateur de pH produit un signal visible en réponse à ladite augmentation de pH.

55 2. Sonde de pH selon la revendication 1, qui se présente sous la forme d'un disque à insérer dans une poche de drainage d'un système de drainage par cathéter.

3. Sonde de pH selon la revendication 1, qui se présente sous la forme d'un anneau doté d'un trou permettant le passage d'un fluide à travers la sonde.

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4. Sonde de pH selon l'une quelconque des revendications précédentes, dans laquelle la matrice polymère est du polyuréthane ou de l'acétate de cellulose.
5. Sonde de pH selon l'une quelconque des revendications précédentes, dans laquelle l'indicateur de pH change de couleur en réponse à une augmentation de pH résultant d'un biofilm bactérien qui se développe sur la surface de la sonde.
6. Sonde de pH selon l'une quelconque des revendications précédentes, dans laquelle l'indicateur de pH change de couleur en réponse à une augmentation du pH de la valeur de pH 6 à pH 7,6 ou plus.
7. Sonde de pH selon l'une quelconque des revendications précédentes, dans laquelle l'indicateur de pH est choisi parmi le pourpre de bromocrésol, le rouge de chlorophénol, le rouge neutre, le bleu de bromothymol, le rouge de crésol, le rouge de m-crésol, le pourpre de m-crésol, le rouge de phénol, le 3-(m-)-nitrophénol, le bleu de thymol, la crésolphtaléine, la fluorescéine, l'acide rosolique et le a-naphtolbenzène.
8. Sonde de pH selon l'une quelconque des revendications précédentes, dans laquelle l'indicateur de pH est le rouge neutre, le bleu de bromothymol, le rouge de crésol, le rouge de phénol, le 3-(m-)-nitrophénol, la fluorescéine et l'acide rosolique.
9. Sonde de pH selon l'une quelconque des revendications précédentes, dans laquelle, en cours d'utilisation, l'indicateur de pH répond à une augmentation du pH lorsque le niveau de pH accru se maintient pendant plus de 6 heures.
10. Sonde de pH selon l'une quelconque des revendications précédentes, dans laquelle, en cours d'utilisation, l'indicateur de pH répond à une augmentation du pH lorsque le niveau de pH accru se maintient pendant plus de 9 heures.
11. Sonde de pH selon l'une quelconque des revendications précédentes, dans laquelle, en cours d'utilisation, l'indicateur de pH répond à une augmentation du pH lorsque le niveau de pH accru se maintient pendant plus de 12 heures.
12. Sonde de pH selon la revendication 1, qui comprend de plus un stabilisateur de matrice.
13. Sonde de pH selon la revendication 12, dans laquelle le stabilisateur de matrice est un composé d'ammonium quaternaire.
14. Sonde de pH selon la revendication 1, dans laquelle la matrice polymère est l'acétate de cellulose et l'indicateur de pH est le bleu de bromothymol.
15. Sonde de pH selon l'une quelconque des revendications précédentes, laquelle est munie d'un matériau de référence pour aider à déterminer le moment auquel l'indicateur de pH a répondu à une augmentation de pH soutenue.
16. Cathéter comprenant une sonde de pH selon l'une quelconque des revendications précédentes.
17. Poche de drainage comprenant une sonde de pH selon l'une quelconque des revendications 1 à 14.
18. Cathéter selon la revendication 16, dans lequel la sonde de pH est positionnée à l'extrémité du cathéter qui, en cours d'utilisation, est raccordé à une unité de drainage.
19. Unité de drainage comprenant une sonde de pH selon l'une quelconque des revendications 1 à 14.
20. Unité de drainage selon la revendication 19, dans laquelle l'unité de drainage comprend une poche de drainage et une tubulaire de poche de drainage et la sonde de pH est positionnée à l'extrémité du tube de poche de drainage qui, en cours d'utilisation, est raccordé au cathéter.
21. Unité de raccordement comprenant la sonde de pH selon l'une quelconque des revendications 1 à 14, dans laquelle l'unité de raccordement peut être insérée entre une unité de drainage et un cathéter.
22. Utilisation de la sonde de pH selon l'une quelconque des revendications 1 à 14 pour prédire l'incrustation et le blocage imminents du cathéter comprenant le positionnement de la sonde de pH dans le flux d'urine à partir d'un cathéter et la surveillance d'un changement au niveau de la sonde de pH indiquant une augmentation de pH soutenue.

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23. Procédé de fabrication d'une sonde de pH selon l'une quelconque des revendications 1 à 14, comprenant l'opération consistant à lier de manière covalente l'indicateur de pH à la matrice polymère, puis à durcir la composition dérivée afin de former la sonde de pH.

5 **24.** Procédé selon la revendication 23, dans lequel la matrice polymère comprend du polyéthylène glycol.

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Figure 1

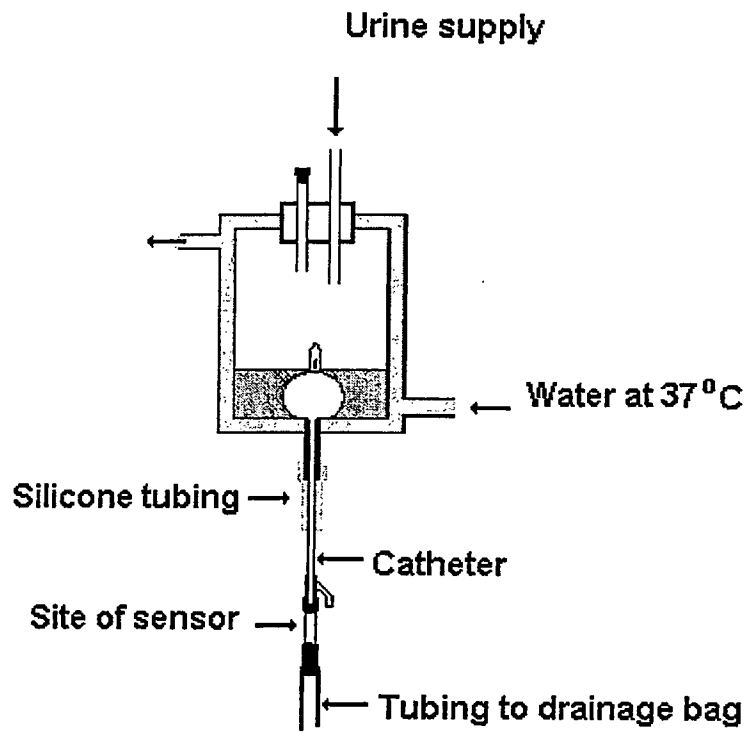


Figure 2

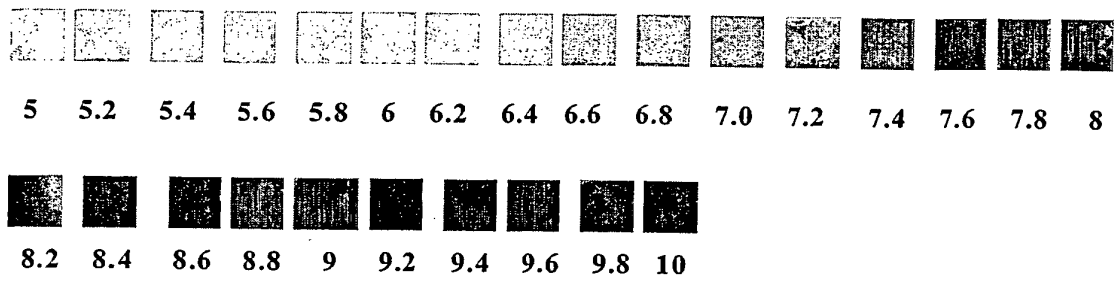


Figure 3

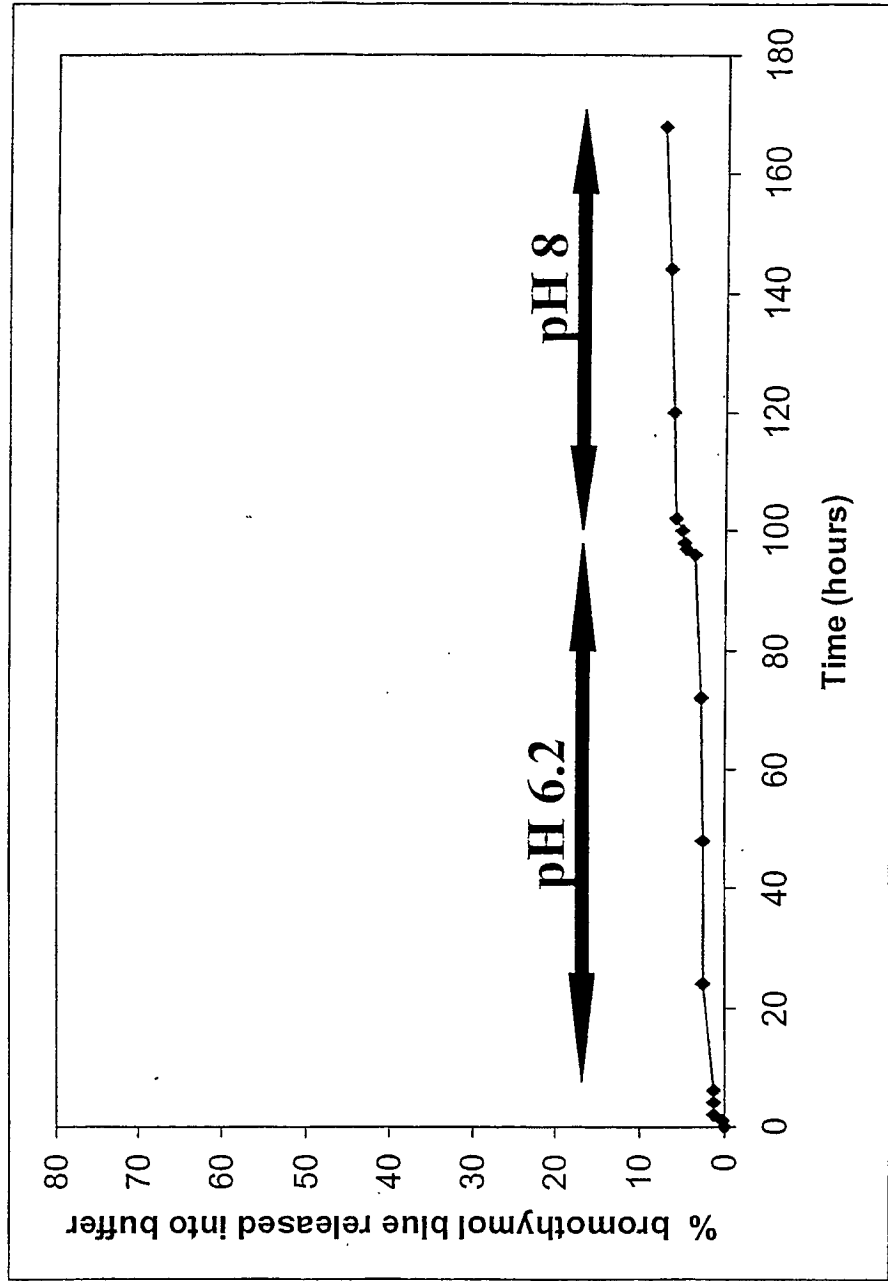


Figure 4

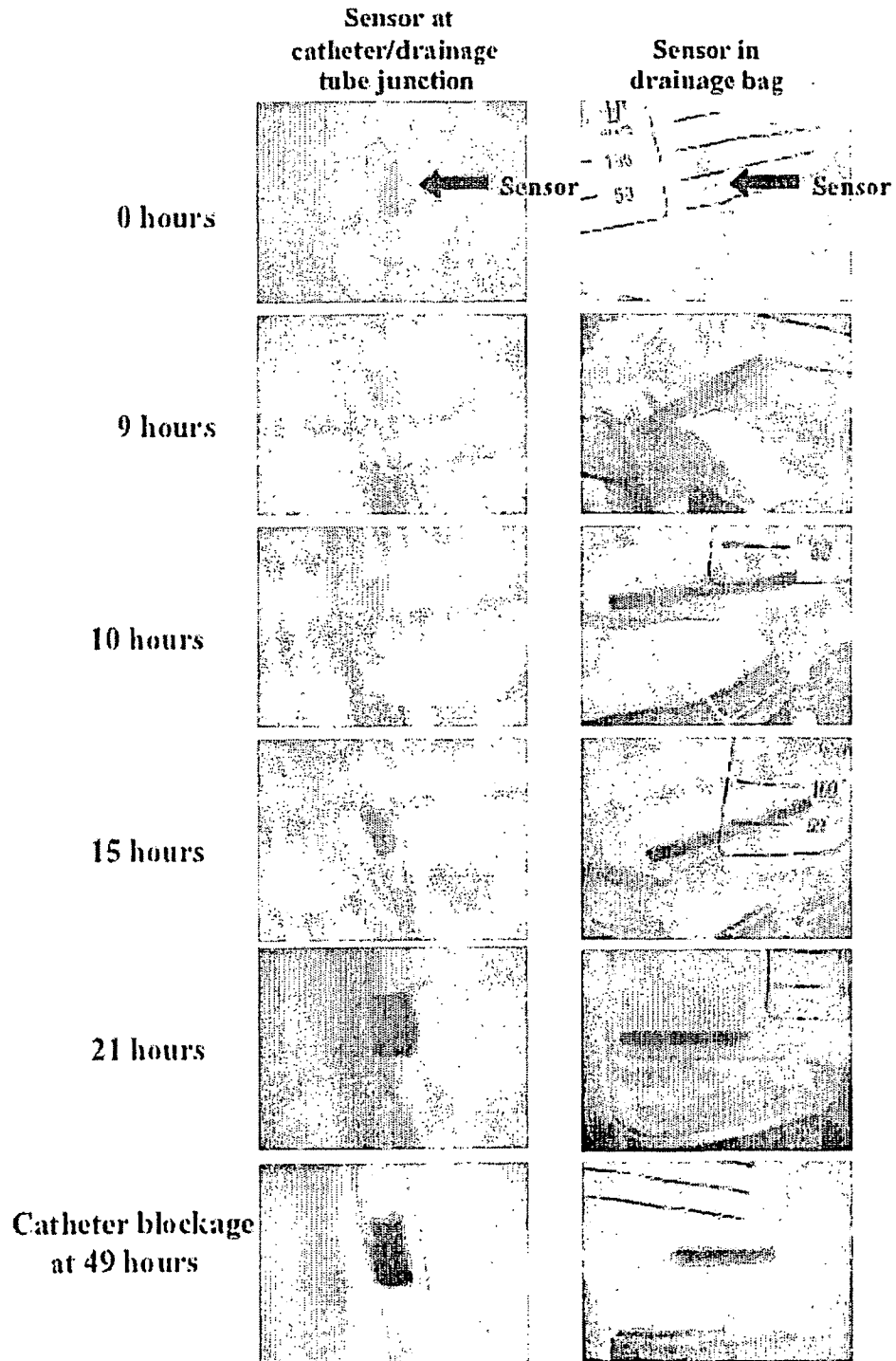


Figure 5A

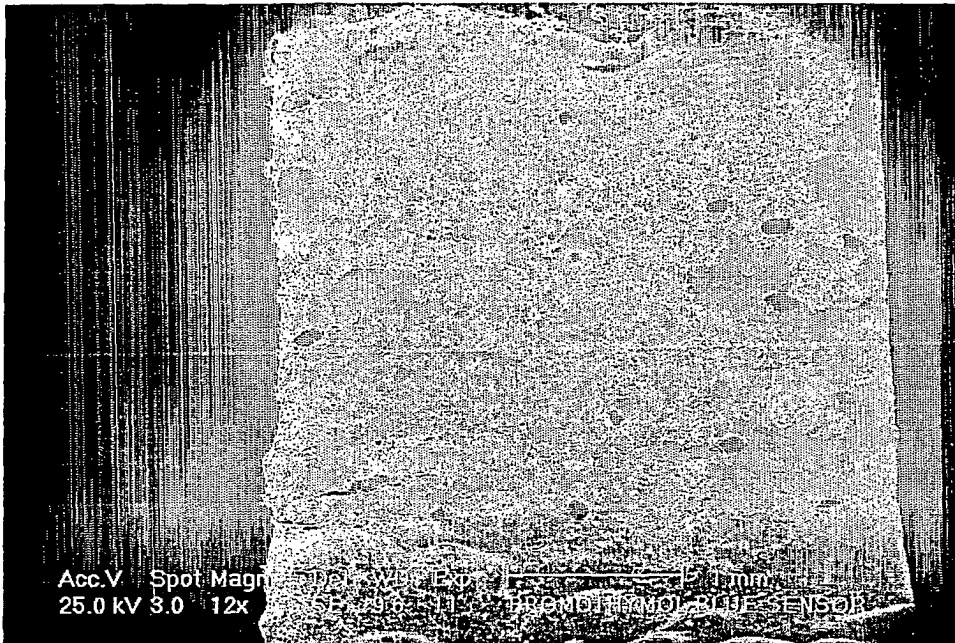
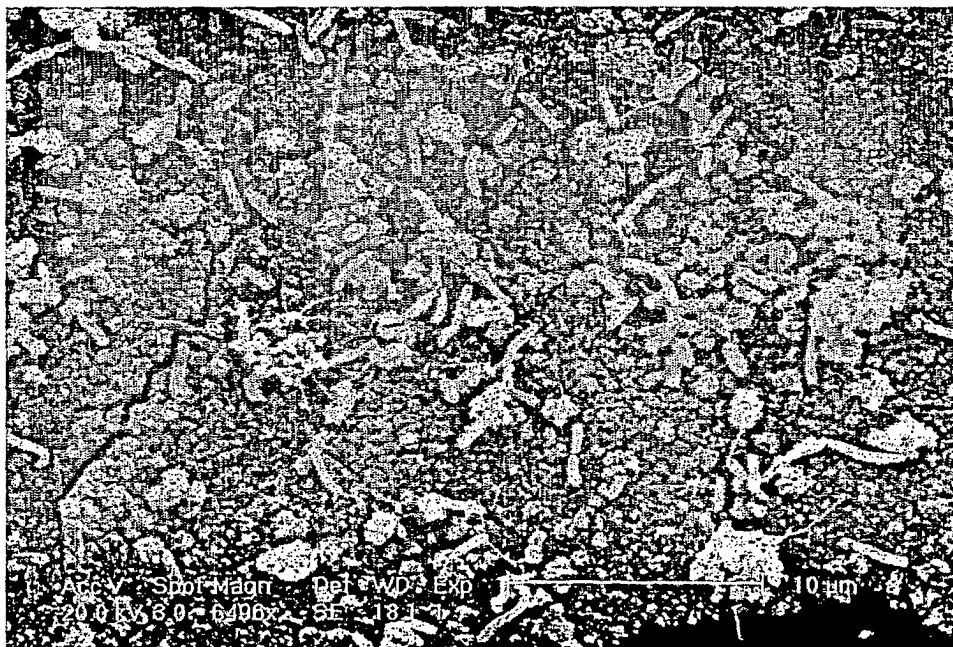


Figure 5B



REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	Ph传感器		
公开(公告)号	EP1761162B1	公开(公告)日	2010-09-01
申请号	EP2005755386	申请日	2005-06-23
申请(专利权)人(译)	大学学院卡迪夫顾问有限公司		
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IPC分类号	A61B5/00 A61M25/00		
CPC分类号	A61B5/6852 A61B5/14539		
代理机构(译)	汤布林, ADRIAN GEORGE		
优先权	2004014222 2004-06-24 GB		
其他公开文献	EP1761162A1		
外部链接	Espacenet		

摘要(译)

本发明涉及一种用于导管引流系统的pH传感器。本发明还涉及包括本发明的pH传感器的导管，引流袋或连接单元，使用pH传感器的方法和制造pH传感器的方法。

Figure 1

