

(19)



(11)

**EP 2 510 958 B1**

(12)

**EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:  
**22.07.2015 Bulletin 2015/30**

(51) Int Cl.:  
**A61M 1/36<sup>(2006.01)</sup> A61B 5/00<sup>(2006.01)</sup>**

(21) Application number: **11161916.9**

(22) Date of filing: **11.04.2011**

**(54) Method and apparatus for monitoring a treatment of a patient, preferably for monitoring hemodialysis, hemodiafiltration and/or peritoneal dialysis**

Verfahren und Vorrichtung zur Überwachung einer Behandlung eines Patienten, vorzugsweise zur Überwachung einer Hämodialyse, Hämodiafiltration und/oder Peritonealdialyse

Procédé et appareil de surveillance du traitement d'un patient, de préférence pour la surveillance de l'hémodialyse, de l'hémodiafiltration et/ou de la dialyse péritonéale

(84) Designated Contracting States:  
**AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(43) Date of publication of application:  
**17.10.2012 Bulletin 2012/42**

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**Description**Technical Field

5 [0001] The present invention pertains to a method and an apparatus for monitoring a treatment of a patient, preferably for monitoring hemodialysis, hemodiafiltration and/or peritoneal dialysis.

Technical Background

10 [0002] Extracorporeal treatment methods have been used for a long time for treating different conditions. Dialysis is the most commonly known and used extracorporeal treatment method which is intended to replace the function of the kidneys when a renal failure of the kidneys occurred in a patient.

15 [0003] When the kidneys fail, dialyzing a patient is necessary to remove waste products such as urea, creatinine and uremic toxins from the blood of the patient. Furthermore, during dialysis, excess water and other substances which are usually eliminated by urine are removed from the body of the patient. The most commonly used method of dialysis is hemodialysis in which the blood of the patient flows along a dialyzing membrane, wherein on the other side of this dialyzing membrane a dialyzing liquid is provided. Accordingly, blood and dialyzing liquid are separated by the porous membrane.

20 [0004] Through this membrane, the substances which are to be removed from the blood of the patient diffuse because of a concentration gradient between blood and the dialyzing liquid. Larger molecules, whose diffusion velocity is very slow, can also be transported convectively by means of a liquid flow from the blood side to the dialysis liquid side of the membrane.

25 [0005] The dialysis liquid is prepared to have a concentration which provides for a concentration gradient from the blood side to the dialysis liquid side for certain substances, but not necessarily for all substances. In fact, the removal of urea and creatinine as well as other waste products in the human body is desired but, for example, the removal or change of concentration of electrolytes such as potassium, sodium or bicarbonate is not at all desired but is considered harmful. Accordingly, the dialysis liquid typically contains a concentration of the electrolytes which resembles the concentration of electrolytes in the blood plasma of the patient such that a concentration gradient is not present for these substances.

30 [0006] Besides the hemodialysis, peritoneal dialysis is another dialysis method which also uses a membrane and a dialysis liquid in order to achieve a diffusion of the waste product through the membrane into the dialysis liquid. The membrane, however, is a natural membrane namely the peritoneum and the dialysis liquid is introduced directly into the abdominal cavity.

35 [0007] During dialysis, the elimination of excess water and small molecular uremic substances such as urea and creatinine is typically no problem, larger molecules, however, are more difficult to remove through the porous membrane. In order to tackle this, specific high flux dialysis membranes are provided in combination with highly convective methods, such as hemodiafiltration. This results in improvements in the clearance of molecules of molecular masses over 1kDa, which is the range of the so-called middle-sized molecules. In hemodiafiltration, a diffusion method using the dialysis liquid in the form as described above is combined with hemofiltration, in which the blood of a patient is subjected to a pressure gradient across a filter. Accordingly, the filtration process along the pressure gradient leads to an increased liquid flow and is, thus, considered a highly convective method which enables the removal of a considerable portion of middle-sized molecules. However, due to the pressure gradient, water as well as electrolytes and sugars are also removed from the blood of the patient at a high rate such that these blood constituents have to be replaced by means of the infusion of a replacement fluid.

45 [0008] The introduction of the high flux dialysis membranes in combination with highly convective methods improves the clearance for middle-sized and larger molecules.

50 [0009] Larger molecules are typically proteins, wherein, for example, beta2-microglobulin has a size of about 11kDa, wherein this molecule may induce an amyloidosis if not sufficiently removed. Smaller molecules which are toxic may also be difficult to dialyze if the molecules are bound to proteins. For example, uremic toxins which are bound to proteins are p-cresyl sulfate and indoxyl sulfate.

55 [0010] Accordingly, it is desired to have pore sizes in the dialysis membranes which are sufficiently large to let through these middle-sized molecules. On the other hand, the pore size of the membrane cannot be extended infinitely, because the higher the pore size of the membrane, the higher the risk that vital blood components are likewise lost. Accordingly, the permeability of the membrane is typically limited to sizes of around 60kDa. However, this value is just slightly below the molecular mass of human plasma albumin which has a size of about 66kDa. In practice, clinically significant losses of albumin may happen wherein these losses significantly depend on the respective parameters of the method, such as the respective pressures and the respective concentrations in the dialysis liquid. In particular, a high flux membrane in combination with the pressure gradient applied during hemofiltration increases the clearance of human albumin. Another

reason for the loss of human albumin may be the multiple use of the membranes because the cleaning of the membrane which is necessary between different treatments tends to increase the sizes of the pores in the membrane. This shifts the permeability of the membrane towards higher molecules. Accordingly, even under normal conditions in normal hemodialysis, human serum albumin may penetrate through the membrane.

5 [0011] It goes without saying that in the case of the peritoneal dialysis the sizes of the pores of the membrane cannot be influenced but are given by the condition of the peritoneum of the respective patient. However, a loss of human albumin into the dialysis liquid may nevertheless take place once the peritoneum has been impaired, for example, by an inflammation.

10 [0012] In order to determine the clearance of an analyte during dialysis, a Raman spectroscopy method is disclosed in US 2008/0158544 A1, wherein the Raman spectral measurements are carried out on the blood after it has passed the dialyzer in order to utilize the unique Raman spectroscopic signature of one or more analytes, e.g., urea, to identify and quantify such analytes against a whole blood background.

15 [0013] WO 2010/091826 A1 relates to an apparatus for the extracorporeal treatment of blood, wherein the absorption of electromagnetic radiation in the dialysis liquid is measured in order to determine the Kt/V value, namely the clearance K of the volume flow of the clean substances, wherein t is the treatment time and V the distribution volume of the patient. In renal replacement therapy, urea is typically used as a marker substance for measuring treatment efficiency, such as ureic acid, such that K is the uric acid clearance and V the urea distribution volume of the patient, which corresponds, in principle, to the body water of the patient. However, by measuring the total absorption, in general the clearance for a specific molecule cannot be determined.

20 [0014] WO 2008/136548 A1 pertains to a device of measuring and monitoring a hemoglobin value through a blood tube.

#### Summary of the disclosure

25 [0015] Accordingly, it is an object of the present invention to provide a method and an apparatus for monitoring a treatment of a patient.

[0016] Protection is sought for the method and apparatus as claimed.

30 [0017] According to the present invention, a method for monitoring a treatment of a patient, preferably for monitoring hemodialysis, hemodiafiltration and/or peritoneal dialysis, is suggested. The method comprises the steps of irradiating a sample of a dialysis liquid used in the treatment with irradiation light of at least a first irradiation wavelength, detecting light emitted by the irradiated sample in at least a first detection wavelength, the detection wavelength being different from the first irradiation wavelength, and determining the presence and/or concentration of at least one analyte in the sample on the basis of the detected emission light.

35 [0018] By means of the irradiation of the sample of dialysis liquid with light of at least a first irradiation wavelength and the detection of light of at least a first detection wavelength, wherein the detection wavelength is different from the first irradiation wavelength, it becomes possible to determine the emission response of an analyte in the dialysis liquid. The presence and/or concentration of specific analytes, such as human albumin, can be monitored in the dialysis liquid in order to monitor the treatment of the patient. In case, for example, that the concentration of the human albumin in the dialysis liquid exceeds a predetermined concentration, an alarm might be released and the replacement of the dialysis membrane might be required. On the other hand, the concentration of uremic toxins such as beta2-microglobulin can be used to monitor and optimize the treatment efficiency by adjusting the treatment modalities.

40 [0019] The detected light includes fluorescence light and the presence and/or concentration of the at least one analyte in the sample is determined on the basis of the detected fluorescence light.

45 [0020] To illustrate this, in fluorescence spectroscopy, a sample is irradiated with irradiation light of a predetermined wavelength. The light beam of the irradiation light, usually ultraviolet light, excites the electrons of certain analytes to a higher energy level. By the absorption of a photon, the molecule is excited from its ground electronic state to one of the various vibrational states in the excited electronic state. When, after a short time, the molecule relaxes again into the ground electronic state, a photon is emitted. Because a portion of the energy is dissipated by means of non-radiating transitions, for example collisions with other molecules which cause the excited molecule to lose vibrational energy, the photon emitted in the process has a lower energy and, thus, a longer wavelength than the exciting photon. Accordingly, the irradiation wavelength of the light exciting the molecule is different from the detection wavelength of the emitted photon such that the irradiation light and the emitted light can be easily distinguished spectroscopically.

50 [0021] Because the excitation wavelength as well as the emission wavelength can be chosen relatively freely in comparison to absorption spectroscopy, more detailed information on the analytes dissolved in the dialysis liquid can be obtained by means of the method. Furthermore, as the intensity of the detected light is typically proportional to the concentration of the analyte or, specifically, of the fluorophore in the dialysis liquid, the intensity of the detected light may serve as a measure for the actual concentration of the respective analyte in the dialysis liquid.

55 [0022] The detection wavelength is different from each of the irradiation wavelengths. This has the advantage that the setup for detecting the light can be simplified because the detection is always carried out at wavelengths different from

the irradiation such that the irradiation light can be blocked from entering the detector by means of devices known in the art.

**[0023]** For example, the fluorescence intensity is proportional to the product of the absorption coefficient  $\epsilon$  at the excitation wavelength and the quantum yield  $\Phi_F$ . The latter refers to the ratio of the absorbed photons to the number of photons emitted by means of fluorescence.

**[0024]** By means of the determination of the presence and/or concentration of at least one analyte in the sample on the basis of the detected light, on the basis of the fluorescence of the respective analyte, the presence and/or concentration of specific molecules can be determined. It is advantageous vis-à-vis the conventional absorption measurement that only a small number of molecules which are present in the dialysis liquid are active with respect to light emission, for example fluorescence. In particular, the substances such as uric acid, which are present in the dialysis liquid in very high concentrations, do not show any fluorescence and do not disturb, therefore, the measurement of the specific molecules. Proteins and the above mentioned uremic toxins, however, can be determined by means of a fluorescence measurement particularly well.

**[0025]** In comparison with absorption spectroscopy, fluorescence spectroscopy is much more sensitive. In fact, when comparing the present method to absorption spectroscopy where very low concentrations of certain components lead only to minor absorption and thus to very small attenuation of the light sent through the sample, the present method has the advantage that the intensity of the fluorescence light is directly proportional to the concentration of the respective analyte in the sample such that the sensitivity of a sensor/detector can be used in an optimum manner.

**[0026]** Exemplary groups of proteins which are fluorescence active are the aromatic side chains of the amino acids phenylalanine, tyrosine and tryptophan.

**[0027]** When considering the fluorescence activity of these amino acids, tyrosine and tryptophan dominate the fluorescence of the proteins. With a sufficiently long excitation wavelength, namely an excitation wavelength of  $\lambda_{ex} \geq 295 \text{ nm}$ , tryptophan is the only amino acid which is fluorescence active. Even though tryptophan is an amino acid which is relatively rare, the albumin molecule includes one tryptophan unit. Due to the high fluorescence efficiency of tryptophan, albumin can thus be detected with sufficient efficiency.

**[0028]** In order to increase the accuracy of the method, the detection light is detected in at least a first detection wavelength and a second detection wavelength, the first and second detection wavelengths being different from one another. Preferably, the detection light is detected by detecting a portion or the entire spectrum of the emitted light of the sample. By detecting more than one wavelength of the emitted light, the correlation of the detection light and a corresponding emission fingerprint, in particular a fluorescence fingerprint, of a specific analyte becomes even more accurate. The emission spectrum for a specific irradiation wavelength can be compared with specific emission fingerprints of the analytes which are relevant, in particular with the emission fingerprints of specific molecules of interest which are intended to be monitored in the extracorporeal treatment method. In fact, it is interesting to monitor, in the dialysis liquid, the presence and/or concentration of free fluorescent amino acids, of albumin, of indoxyl sulfate and of any other fluorescent uremic toxins in order to determine the clearance for the respective molecules.

**[0029]** As a supplement to the analysis of fluorescence light, Raman scattered light may be used for the determination of the presence and/or concentration of a certain analyte in the sample. To this end, the Raman emission of the sample is measured either over the whole Raman spectrum, over a portion thereof or over certain detection wavelengths and the respective intensities or spectra are compared to Raman fingerprints of the respective analytes of interest.

**[0030]** In order to further increase the accuracy of the determination of the presence and/or concentration of the analyte, the sample is irradiated by an irradiation light in the UV-range, with irradiation light having a wavelength of between 180 nm and 400 nm, more preferably at 250 nm to 300 nm, most preferred at 280 nm and/or 295 nm. Preferably, the sample is irradiated with irradiation light of at least two separated, distinct irradiation wavelengths, preferably at 280 nm and 295 nm. The two different emission spectra induced by the two irradiation wavelengths may be compared and the efficiency and accuracy of the determination of the analyte be even more increased.

**[0031]** In order to compensate for absorption of the irradiation light in the sample, the intensity of the irradiation light in the sample is preferably determined and the determination of the presence and/or concentration of the analyte in the sample is compensated for the intensity of the irradiation light. Preferably the absorption of the irradiation light in the sample is measured and the intensity of the irradiation light is determined on the basis of the measured absorption, wherein preferably the absorption in the sample is measured by means of a photo detector detecting the irradiation light transmitted through the sample.

**[0032]** Alternatively, the intensity of Raman scattered light of the sample is measured and is used to determine the intensity of the irradiation light. This measurement of the Raman scattered light may be carried out at the intensity peak of the Raman scattered light in water.

**[0033]** The step of compensating for the absorption of light in the sample takes care of the fact that the dialysis liquid may have a different absorption, depending on the efficiency of the dialysis process as well as on the basis of the different conditions of the respective patient. In fact, at the beginning of a dialysis session, the dialysis liquid may contain a significantly higher proportion of uric acid, creatinine and other waste products which have a high absorption for the excitation light than in a later status of the dialysis process. In order to be in a position to safely determine the presence

and/or concentration of the respective analyte in the sample, it is important to determine the respective absorption of the sample such that it is clear what is the actual excitation intensity which results in the respective fluorescence spectrum and the respective fluorescence intensity.

**[0034]** Even further information on the presence and/or concentration of an analyte in the sample can be obtained when preferably detecting the fluorescence light in a time resolved manner, preferably wherein the irradiation light is pulsed.

**[0035]** Other forms of analysis of the analytes may be present by irradiating the sample with polarized light, preferably with left-handed circularly polarized light and/or right-handed circularly polarized light.

**[0036]** In order to further improve the method, the fluorescence light of the sample is preferably detected at least twice, wherein between the first and second detections the sample is treated physically and/or chemically and the presence and/or concentration of the analyte is determined taking into account the difference between the first and second detections, wherein the sample is preferably treated by heating, by adding and/or removing of reagents and/or by adding and/or removing of an acid, of a chemical base and/or of a salt.

**[0037]** To be in a position to carry out more complex measurements, the sample may be separated from the flow of dialysis liquid for carrying out the determination of the presence and/or concentration of the analyte.

**[0038]** In an alternative, the determination of the presence and/or concentration of the analyte may be carried out continuously on the flow of dialysis liquid.

**[0039]** In yet another preferred version, before irradiating the sample with the irradiation light, the sample is separated into different fractions, preferably by means of ultrafiltration, electrophoresis, chromatography, the addition of absorber and/or the addition of a fluorescent marker, and at least one of the fractions of the sample is irradiated with the irradiation light.

**[0040]** When monitoring the analyte in the dialysis liquid, in particular when monitoring the presence and/or absence of albumin, it can be seen that human albumin emits a fluorescent light which has a maximum at 340 nm when it is excited at about 280 nm.

**[0041]** Indoxyl sulfate (indican) which is a waste product of tryptophan, is known to be present in uremic patients in a significant concentration in the blood serum. Indoxyl sulfate is known to be a uremic toxin. The fluorescence spectra of tryptophan and indoxyl sulfate are considerably similar such that, besides the proteins of the dialysis, the clearance of indoxyl sulfate is interesting in diagnostic aspects. As an alternative, fluorescence markers binding to certain molecules may be used to determine the presence and/or concentration of the respective molecules.

**[0042]** In order to even more precisely determine the composition of the used dialysis liquid, the presence and/or concentration of at least two different analytes may be determined on the basis of the detected light.

**[0043]** Preferably, after excitation with a specific wavelength by irradiation of the sample with the irradiation light, the detected light may be analysed as to the presence of the at least N different analytes. This is done by analyzing the detected spectrum  $f(\lambda)$ , i.e. the intensities at the respective emission wavelength  $\lambda$ , which is assumed to be given in the form of a linear superposition of the emission spectra of the N analytes:

$$f(\lambda) = \sum_{i=1}^N c_i s_i(\lambda)$$

$C_i$  being the unknown concentration of the  $i^{\text{th}}$  analyte and  $S_i(\lambda)$  being the known emission sensitivity of the  $i^{\text{th}}$  analyte as a function of the respective emission wavelength  $\lambda$ . This equation is preferably solved for the unknown concentrations  $C_i$  by determining the spectrum at M different discrete emission wavelengths  $\lambda_j$ , considering the above equation in the form of the following system of M equations with N unknowns:

$$\begin{pmatrix} f(\lambda_1) \\ f(\lambda_2) \\ \vdots \\ f(\lambda_M) \end{pmatrix} = \begin{pmatrix} s_1(\lambda_1) & s_2(\lambda_1) & \cdots & s_N(\lambda_1) \\ s_1(\lambda_2) & s_2(\lambda_2) & \cdots & s_N(\lambda_2) \\ \vdots & \vdots & \ddots & \vdots \\ s_1(\lambda_M) & s_2(\lambda_M) & \cdots & s_N(\lambda_M) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ \vdots \\ c_N \end{pmatrix}$$

**[0044]** This system is solved numerically, preferably by considering as the best solution for the above system of equations the one which provides, when being inserted into the above matrix, the superposition spectrum which has the lowest square deviation from the actually measured spectrum. By means of this analysis it becomes possible determining the composition of the dialysis fluid by analyzing the detected emission light and in particular by analyzing the respective spectrum of the detected emission light. In particular, the unknown concentrations  $C_i$  are determined and, thus, the

composition of the used dialysis fluid with respect to the concentrations  $C_i$  of the respective analytes can be determined.

**[0045]** This method can be extended to more than one, namely  $P$ , irradiation wavelengths  $\lambda_{irr}$ ,  $P$  being larger than one, when for each irradiation wavelength  $\lambda_{irr}$  a separate emission spectrum  $f(\lambda_{irr}, \lambda)$  is detected at the respective emission wavelength  $\lambda$ . Accordingly, the detected spectrum  $f(\lambda_{irr}, \lambda)$  for one irradiation wavelength  $\lambda_{irr}$  is assumed, again, to be given in the form of a linear superposition of the emission spectra of the  $N$  analytes:

$$f(\lambda_{irr}, \lambda) = \sum_{i=1}^N c_i s_i(\lambda_{irr}, \lambda)$$

$C_i$  being the unknown concentration of the  $i^{\text{th}}$  analyte and  $S_i(\lambda_{irr}, \lambda)$  being the known emission sensitivity of the  $i^{\text{th}}$  analyte as a function of the emission wavelength  $\lambda$  at the respective irradiation wavelength  $\lambda_{irr}$ .

**[0046]** By adding the respective equations to the linear equation system given above, it reads:

$$\begin{pmatrix} f(\lambda_{irr1}, \lambda_1) \\ f(\lambda_{irr1}, \lambda_2) \\ \vdots \\ f(\lambda_{irr1}, \lambda_M) \\ f(\lambda_{irr2}, \lambda_1) \\ f(\lambda_{irr2}, \lambda_2) \\ \vdots \\ f(\lambda_{irr2}, \lambda_M) \\ \vdots \\ f(\lambda_{irrP}, \lambda_1) \\ \vdots \\ f(\lambda_{irrP}, \lambda_M) \end{pmatrix} = \begin{pmatrix} s_1(\lambda_{irr1}, \lambda_1) & s_2(\lambda_{irr1}, \lambda_1) & \dots & s_N(\lambda_{irr1}, \lambda_1) \\ s_1(\lambda_{irr1}, \lambda_2) & s_2(\lambda_{irr1}, \lambda_2) & \dots & s_N(\lambda_{irr1}, \lambda_2) \\ \vdots & \vdots & \dots & \vdots \\ s_1(\lambda_{irr1}, \lambda_M) & s_2(\lambda_{irr1}, \lambda_M) & \dots & s_N(\lambda_{irr1}, \lambda_M) \\ s_1(\lambda_{irr2}, \lambda_1) & s_2(\lambda_{irr2}, \lambda_1) & \dots & s_N(\lambda_{irr2}, \lambda_1) \\ s_1(\lambda_{irr2}, \lambda_2) & s_2(\lambda_{irr2}, \lambda_2) & \dots & s_N(\lambda_{irr2}, \lambda_2) \\ \vdots & \vdots & \dots & \vdots \\ s_1(\lambda_{irr2}, \lambda_M) & s_2(\lambda_{irr2}, \lambda_M) & \dots & s_N(\lambda_{irr2}, \lambda_M) \\ \vdots & \vdots & \dots & \vdots \\ s_1(\lambda_{irrP}, \lambda_1) & s_2(\lambda_{irrP}, \lambda_1) & \dots & s_N(\lambda_{irrP}, \lambda_1) \\ \vdots & \vdots & \dots & \vdots \\ s_1(\lambda_{irrP}, \lambda_M) & s_2(\lambda_{irrP}, \lambda_M) & \dots & s_N(\lambda_{irrP}, \lambda_M) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \end{pmatrix}$$

**[0047]** By solving the above equation system, preferably in the same fashion as indicated above, a solution for the concentrations  $C_i$  can be determined and, thus, the concentrations of the respective analytes in the used dialysis liquid can be determined.

**[0048]** The objective given above is also solved by means of an apparatus for monitoring a treatment of a patient, preferably for monitoring hemodialysis, hemodiafiltration and/or peritoneal dialysis, with the features of claim 1.

**[0049]** Accordingly, the apparatus for monitoring a treatment of a patient, preferably for monitoring hemodialysis, hemodiafiltration and/or peritoneal dialysis, the apparatus comprises a light source for irradiating a sample of a dialysis liquid used in the treatment with irradiation light of at least a first irradiation wavelength, a detector for detecting light emitted by the irradiated sample in at least a first detection wavelength, the detection wavelength being different from each irradiation wavelength, and a control and analysis unit for determining the presence and/or concentration of at least one analyte in the sample on the basis of the detected light.

**[0050]** Further preferred embodiments of the apparatus are given in the claims dependent on independent apparatus claim 12.

Brief description of the drawings

**[0051]** The present disclosure will be more readily appreciated by reference to the following detailed description when being considered in connection with the accompanying drawings in which:

Figure 1 is a schematic view of an apparatus for monitoring an analyte in an extracorporeal treatment;

Figure 2 is a schematic detailed view of a portion of the apparatus according to Figure 1;

Figure 3 is a schematic diagram showing the fluorescence spectrum of human albumin in different concentrations after excitation at an irradiation wavelength at 280nm;

Figure 4 is a schematic diagram showing the fluorescence intensity of albumin at a detected light wavelength of 340 nm at two different irradiation wavelengths, namely at 280nm and at 295nm; and

Figure 5 is a schematic diagram showing the absorption spectrum of uric acid.

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#### Detailed description of the preferred embodiments

[0052] In the following, the disclosure will be explained in more detail with reference to the accompanying Figures. In the Figures, like elements are denoted by identical reference numerals and repeated description thereof may be omitted in order to avoid redundancies.

10

[0053] Figure 1 is a schematic view of a system for treating a patient, in particular an apparatus for dialysis. The system includes an apparatus for monitoring the treatment of a patient.

[0054] In particular, Figure 1 shows a dialyzer comprising a porous, semi-permeable membrane 3. On the right-hand side of Figure 1 the blood circulation of the patient is connected to the membrane 3 and on the left-hand side the dialyzing liquid circulation is connected to the membrane 3. The principle of hemodialysis is well known and involves the diffusion of solutes in the blood through the semi-permeable membrane 3. The diffusion is induced by a concentration gradient of certain substances across the membrane 3.

15

[0055] Blood from the patient is transported via conduit 1 to the membrane 3 and passes along the membrane on one side of it towards conduit 2, from which the blood is transported back to the patient.

20

[0056] The dialyzing liquid is transported via conduit 4 to the membrane 3 and is discarded via conduit 5. From Figure 1, it becomes immediately apparent that, in this specific embodiment, the blood circulation and the dialyzing liquid circulation involve opposing fluid streams on the membrane 3. The method utilizes counter current flows such that fresh dialyzing liquid comes in contact with the blood of the patient that is going to be transported back to the patient again and fresh blood from the patient comes in contact with the dialyzing liquid that is about to be discarded. This is standard practice to increase the efficiency of the dialyzing process because the counter current flow maintains the concentration gradient across the membrane at a maximum and increases the efficiency of the dialysis. However, in alternative solutions a parallel flow of blood and dialysis fluid may also be used, depending on the therapeutic needs of the patient.

25

[0057] The membrane 3 is a porous, semi-permeable membrane as is customary when in dialysis apparatus. Due to the concentration gradient between the patient side and the dialysis liquid side of the membrane 3, molecules diffuse from the blood side through the semi-permeable membrane 3 to the dialysis liquid side and are, such, removed from the blood.

30

[0058] Depending on the actual conditions of the patient and depending on the effect that is intended to be achieved, the dialysis liquid includes concentrations of different substances which are intended to match the concentrations in the blood, such that a concentration gradient is not present. This may be the case, for example, for electrolytes which consequently do not diffuse through the membrane 3. However, other substances may not at all be present in the fresh dialysis liquid such that a strong concentration gradient is induced. This strong concentration gradient is desired, in particular, for substances which are normally eliminated via urine such as uric acid, creatinine and the uremic toxins. Excess water in the blood is also intended to be removed. Depending on the sizes of the pores of the membrane 3, however, diffusion of larger molecules such as, for example, human albumin might also occur. This is, however, not desired.

35

[0059] A sample of the used dialysis liquid, which is discharged via the conduit 5, is analyzed in a cell 6 with respect to the presence and/or concentration of at least one analyte. To this end, a light source 7 is present which irradiates the sample of dialysis liquid present in the cell 6 with an excitation light. The light source 7 preferably emits at least one first wavelength, preferably a wavelength of light in the ultraviolet range, namely in a range between 180 nm and 400 nm. In the specific embodiment shown in Figure 1, the light source 7 is a semi-conductor based light source for the ultraviolet range, in particular an AlInGaN-diode emitting light at a wavelength of 280 nm. However, any other suitable light source may be used.

45

[0060] The sample of dialysis liquid present in cell 6 is illuminated by the light which impinges on it and which is emitted from the light source 7. The photons of the light excite certain molecules present in the dialysis liquid such that the emission of fluorescence light may be induced in the sample. The presence, wavelength and intensity of the fluorescence light is detected by means of a detector in form of a spectrometer 9 in a direction perpendicular to the illumination direction of the light emitted from the light source 7. Any other direction which is other than being co-axial with the illumination direction of the light source 7 could be used for detecting the fluorescence light induced in the selected molecules in the dialysis liquid in the cell 6. A co-axial arrangement of the spectrometer would typically result in a strong distortion by the irradiation light but it may also be possible using filters, reflection gratings or a wavelength dependent beam splitters to divide the detected light emitted from the sample from the illumination light. As the wavelengths of the illumination light and the detected light are different from one another, many devices for dividing the different light beams from one another are known in the art.

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**[0061]** The intensity of the emitted fluorescence light and, in a preferred embodiment, a portion or the entire fluorescence spectrum is detected by means of the spectrometer 9. In an alternative when only selected emission wavelengths are of interest, filters or other wavelength selective devices could also be present in place of the spectrometer 9 in order to select specific wavelengths to be analysed as to their intensity.

5 **[0062]** As, in a preferred embodiment, the detection wavelength is different from each of the irradiation wavelengths, the light emitted from the sample can be detected easily by simply blocking the irradiation light from entering into the detector by means of devices known in the art.

10 **[0063]** This intensity data of the emitted and detected light is communicated to a control and analysis unit 11. In the control and analysis unit 11 the presence and/or concentration of at least one analyte in the sample present in the cell 6 is determined on the basis of the information as to the irradiation wavelength and irradiation intensity, as well as the intensity and wavelength of the detected fluorescence light detected by the spectrometer 9. Each fluorescent molecule has a specific fingerprint as to its fluorescent light spectrum for a specific irradiation wavelength.

**[0064]** This determination can be carried out in different ways, one of which is described further below.

15 **[0065]** In the apparatus shown in Figure 1, furthermore, a photo detector 8 is present which is located in a co-axial manner with the irradiation light beam emitted from the light source 7. The photo detector 8 is situated on an opposite side of the light source 7 with the cell 6 in-between and consequently receives the irradiation light of the light source 7 which has passed through the cell 6. In other words, the photo detector 8 is intended to detect the light intensity of the light which has been transmitted through the cell 6 and, thus, which has been partly absorbed and is, thus, attenuated by the sample present in the cell 6. The intensity of light received by the photo detector 8 is also communicated to the control and analysis unit 11.

20 **[0066]** In order to be in a position to carry out a calibration of the relationship of the light source 7 and the photo detector 8, as well as a calibration of the spectrometer 9, a bypass valve 10 is present, which can be controlled by means of the control and analysis unit 11. By opening the bypass valve 10, fresh dialysis liquid can be delivered to the cell 6 such that only fresh dialysis liquid is present in the cell 6. As soon as the bypass valve 10 is shut again, the dialysis liquid circulates through the filter 3 and the cell 6 receives used dialysis liquid again.

25 **[0067]** The control and analysis unit 11 may determine the presence and/or concentration of a specific analyte, for example human albumin, in the dialysis liquid on the basis of the fluorescence light received by the spectrometer 9. This can be done, for example, by comparing the fluorescence spectrum measured by the spectrometer 9 with a fluorescence spectrum of a specific molecule - a so called fluorescence fingerprint - which may be stored in a storage 12 in Figure 1. By comparing the measured fluorescence spectrum with a finger print of a specific molecule, the presence of a specific analyte can be determined.

30 **[0068]** In order to be in a position to determine the concentration of the analyte, the actual intensity of the spectrum is also of relevance.

35 **[0069]** Even though in the present description of the preferred embodiments the focus is on the analysis of fluorescence light as the detected light, analyzing other forms of light emission of an excited sample are also contemplated, such as the analysis of Raman scattered light for the determination of the presence and/or concentration of at least one analyte in the used dialysis fluid. The principles of this determination are comparable to the principles outlined above with respect to the analysis of the fluorescence light.

40 **[0070]** In this respect, Figure 3 shows the fluorescence spectra for human albumin of different concentrations when being excited with light of a wavelength of 280 nm. Four different concentrations of the human albumin are measured in Figure 3, namely concentrations of 7 mg/l, 23 mg/l, 45 mg/l and 98 mg/l. It is immediately apparent from Figure 3 that the maximum fluorescence peak is at approximately 340 nm but that the intensities vary according to the respective concentrations. Figure 4 shows the fluorescence intensity at 340 nm for human albumin at two different excitation wavelengths, namely at 280 nm and at 295 nm.

45 **[0071]** It is contemplated in the apparatus of Figure 1 to excite the sample present in the cell 6 at more than one wavelength, for example at two different wavelengths, in order to even more precisely be in a position to determine the presence of a specific molecule, for example human albumin, and also be in a position to determine the actual concentration of this molecule in the dialysis liquid present in the cell 6.

50 **[0072]** When considering the mechanism of dialysis, it becomes also apparent that it is not only the albumin that will be present in the dialysis liquid in the conduit 5 after it has been passed along the semi-permeable membrane 3, but many other waste products will be present in the dialysis liquid. One is, for example, uric acid.

**[0073]** Uric acid, however, has a specific absorption spectrum which is shown, schematically, in Figure 5. Figure 5 is taken from "Photoelectric Spectrometry Group, London; Institut für Spektrochemie und Angewandte Spektroskopie, Dortmund (1968): DMS UV Atlas of Organic Compounds. 5 Volumes. Weinheim, London: Verlag Chemie; Butterworths".

55 **[0074]** When considering Figure 5, it becomes apparent that one absorption peak of uric acid is at about 280 nm which corresponds to the excitation wavelength used for measuring the fluorescence intensity of the human albumin shown in Figure 3. Accordingly, the higher the concentration of uric acid in the dialysis liquid, the higher is the absorption of the irradiation light. When the excitation wavelength is set at 280 nm, the intensity which is actually applied to a certain

volume of the dialysis liquid in the cell 6 is strongly attenuated by means of the presence of the uric acid in the dialysis liquid. Uric acid, however, does not emit any fluorescent light. However, in order to be in a position to reliably determine the intensity of the emitted fluorescent light on the basis of the light intensity emitted by the light source 7, the actual attenuation must be determined.

5 [0075] Figure 2 shows an arrangement for compensating for the absorption of the excitation light in the sample present in the cell 6. The intensity of the light source 7 can be easily determined by measuring the light intensity in the cell 6. However, as the concentration of uric acid in the dialysis liquid varies widely during a dialysis session, it needs to be compensated for.

10 [0076] Accordingly, the intensity of the light at the excitation volume can be calculated on the basis of the Lambert-Beer law, dealing with the absorption of light in material through which the light is traveling:

$$I(x) = I_0 e^{-\alpha x}$$

15 [0077] Here,  $I_0$  is the initial intensity of the light impinging on the cell,  $I(x)$  is the intensity after the light has been travelled by a distance  $x$  through the cell 6 and the coefficient  $\alpha$  is a measure for the absorption strength.

[0078] Accordingly, after the light has passed through the entire cell 6 of the length  $L$ , the intensity is:

20 
$$I(L) = I_0 e^{-\alpha L}$$

[0079] Accordingly, assuming that the sample from which the fluorescence light is emitted is distanced by the distance  $l$  from the light entrance into the cell, the intensity in the sample is:

25 
$$I(l) = I_0 e^{-\alpha l}$$

[0080] The photo detector 8 continuously measures the intensity  $I(L)$ , namely the intensity of the light that has travelled through the entire cell 6. Provided the initial intensity  $I_0$  of the light source 7 remains constant, the coefficient  $\alpha$  may be determined such that the light intensity  $I(l)$  in the sample which emits the fluorescence light can be calculated at any time. Accordingly, all fluorescence spectra or fluorescence light can be compensated for the absorption in the dialysis liquid present in the cell 6. In other words, the concentration of the respective analyte can be determined because the intensity  $I(l)$  of the irradiation light in the sample is known.

30 [0081] In an alternative or in addition to the measurement of the absorption, the excitation intensity of the light emitted by the light source 7 can be determined by analyzing the Raman scattering on water molecules present in the sample in the cell 6. To this end, preferably a Raman spectrum of the sample is obtained. In an alternative, it may be sufficient if only the intensity of the Raman scattered light peak on water for the respective irradiation light is measured. In other words, it is sufficient to measure the Raman peak of water for the respective irradiation light in order to determine the damping of the irradiation light in water.

35 [0082] The intensity of the Raman scattering is substantially proportional to the intensity of the excitation light and of the density of the water molecules in the sample. The density of the water molecules in the sample is, however, substantially constant in the dialysis liquid. Accordingly, by obtaining the Raman spectrum of the sample which also emits the fluorescence light it becomes possible determining the excitation intensity present in the sample. The Raman spectrum may be obtained using the spectrometer 9 as well.

40 [0083] The spectrometer 9 used may be a conventional spectrometer which is readily available on the market. Such a spectrometer typically comprises an input lens for focusing the incident light, a diffraction grating and a (line) CCD-camera for detecting the light.

[0084] Fluorescence spectra in a real dialysis liquid are, however, typically not emitted by a single fluorescent molecule only but usually comprise at least two spectra which are superposed. At least the molecules of albumin and indoxyl sulfate must be considered here.

45 [0085] For the purpose of a reliable monitoring of a treatment of a patient it is, however, desirable to know about the presence and/or concentration of more than one analytes in the used dialysis liquid. For example, the medical practitioner is interested in whether human albumin and/or indoxyl sulfate are present in the used dialysis liquid and if any of these analytes is present, the medical practitioner likes to know the concentration thereof.

50 [0086] For the following analysis it is assumed that the fluorescence spectrum which is emitted from the sample after excitation at a specific irradiation wavelength is actually measured by means of the spectrometer 9. The fluorescence spectrum is signified as  $f(\lambda)$  and is considered to be represented by linear superposition of the different fluorescence

spectra of N single fluorophores:

$$f(\lambda) = \sum_{i=1}^N c_i s_i(\lambda)$$

**[0087]** In this equation,  $C_i$  is the concentration of the  $i^{\text{th}}$  fluorophore and  $S_i(\lambda)$  is the respective fluorescence sensitivity of the  $i^{\text{th}}$  fluorophore as a function of the respective emission wavelength  $\lambda$ . If the spectrum is recorded at M different wavelengths  $\lambda_j$ , the above equation can be given as a system of M equations with N unknowns:

$$\begin{pmatrix} f(\lambda_1) \\ f(\lambda_2) \\ \vdots \\ f(\lambda_M) \end{pmatrix} = \begin{pmatrix} s_1(\lambda_1) & s_2(\lambda_1) & \cdots & s_N(\lambda_1) \\ s_1(\lambda_2) & s_2(\lambda_2) & \cdots & s_N(\lambda_2) \\ \vdots & \vdots & \ddots & \vdots \\ s_1(\lambda_M) & s_2(\lambda_M) & \cdots & s_N(\lambda_M) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ \vdots \\ c_N \end{pmatrix}$$

**[0088]** Accordingly, the unknown concentrations  $C_i$  may be calculated from the measured spectral intensities  $f(\lambda_j)$  taking into account the known matrix elements  $S_i(\lambda_j)$ . The matrix elements  $S_i(\lambda_j)$  may be considered representing the "fluorescence fingerprint" of the respective analytes.

**[0089]** The above system of equations can be solved, in particular numerically. For example, the best solution for the above system of equations is considered the one, which provides, when being inserted into the above matrix, the (theoretical) superposition spectrum which has the lowest square deviation from the actually measured spectrum. By means of this analysis it becomes possible determining the composition of the dialysis fluid by analyzing the detected fluorescence light and in particular by analyzing the respective spectrum of the detected fluorescence light. In particular, the unknown concentrations  $C_i$  are determined and, thus, the composition of the used dialysis fluid with respect to the concentrations  $C_i$  of the respective analytes can be determined.

**[0090]** In an alternative, more than one irradiation wavelengths are used in the irradiation light. In particular, P different irradiation wavelengths  $\lambda_{irr}$  are used in this method - for example by providing different irradiation light diodes. For each irradiation wavelength  $\lambda_{irr}$  the intensities  $f(\lambda_{irr}, \lambda)$  are recorded for the respective emission wavelengths  $\lambda$ . The thus detected spectrum  $f(\lambda_{irr}, \lambda)$  for one irradiation wavelength is assumed, again, to be given in the form of a linear superposition of the fluorescence spectra of the N analytes:

$$f(\lambda_{irr}, \lambda) = \sum_{i=1}^N c_i s_i(\lambda_{irr}, \lambda)$$

$C_i$  being the unknown concentration of the  $i^{\text{th}}$  analyte and  $S_i(\lambda_{irr}, \lambda)$  being the known fluorescence sensitivity of the  $i^{\text{th}}$  analyte as a function of the fluorescence wavelength  $\lambda$  at the respective irradiation wavelength  $\lambda_{irr}$ .

**[0091]** By adding the respective equations to the linear equation system given above, it reads:

$$\begin{array}{l}
 5 \\
 10 \\
 15
 \end{array}
 \begin{pmatrix}
 f(\lambda_{irr1}, \lambda_1) \\
 f(\lambda_{irr1}, \lambda_2) \\
 \vdots \\
 f(\lambda_{irr1}, \lambda_M) \\
 f(\lambda_{irr2}, \lambda_1) \\
 f(\lambda_{irr2}, \lambda_2) \\
 \vdots \\
 f(\lambda_{irr2}, \lambda_M) \\
 \vdots \\
 f(\lambda_{irrp}, \lambda_1) \\
 \vdots \\
 f(\lambda_{irrp}, \lambda_M)
 \end{pmatrix}
 =
 \begin{pmatrix}
 s_1(\lambda_{irr1}, \lambda_1) & s_2(\lambda_{irr1}, \lambda_1) & \cdots & s_N(\lambda_{irr1}, \lambda_1) \\
 s_1(\lambda_{irr1}, \lambda_2) & s_2(\lambda_{irr1}, \lambda_2) & \cdots & s_N(\lambda_{irr1}, \lambda_2) \\
 \vdots & \vdots & \cdots & \vdots \\
 s_1(\lambda_{irr1}, \lambda_M) & s_2(\lambda_{irr1}, \lambda_M) & \cdots & s_N(\lambda_{irr1}, \lambda_M) \\
 s_1(\lambda_{irr2}, \lambda_1) & s_2(\lambda_{irr2}, \lambda_1) & \cdots & s_N(\lambda_{irr2}, \lambda_1) \\
 s_1(\lambda_{irr2}, \lambda_2) & s_2(\lambda_{irr2}, \lambda_2) & \cdots & s_N(\lambda_{irr2}, \lambda_2) \\
 \vdots & \vdots & \cdots & \vdots \\
 s_1(\lambda_{irr2}, \lambda_M) & s_2(\lambda_{irr2}, \lambda_M) & \cdots & s_N(\lambda_{irr2}, \lambda_M) \\
 \vdots & \vdots & \cdots & \vdots \\
 s_1(\lambda_{irrp}, \lambda_1) & s_2(\lambda_{irrp}, \lambda_1) & \cdots & s_N(\lambda_{irrp}, \lambda_1) \\
 \vdots & \vdots & \cdots & \vdots \\
 s_1(\lambda_{irrp}, \lambda_M) & s_2(\lambda_{irrp}, \lambda_M) & \cdots & s_N(\lambda_{irrp}, \lambda_M)
 \end{pmatrix}
 \begin{pmatrix}
 c_1 \\
 c_2 \\
 \vdots \\
 \vdots \\
 \vdots \\
 \vdots \\
 \vdots \\
 \vdots \\
 \vdots \\
 \vdots \\
 \vdots \\
 c_N
 \end{pmatrix}$$

20 **[0092]** By solving the above equation system, preferably in the same fashion as indicated above, a solution for the concentrations  $C_i$  can be determined and, thus, the concentrations of the respective analytes in the used dialysis liquid can be determined.

25 **[0093]** In further preferred embodiments, the fluorescence spectra are measured by means of the spectrometer 9 in a time resolved manner. In order to accomplish this, the excitation light emitted from the light source 7 is preferably provided in a non-continuous manner, for example in a pulsed manner. For example, a pulsed laser may be used for probing the sample. By means of the provision of time-resolved fluorescence spectra, further information as to the presence and/or concentration of certain analytes can be derived from the sample.

30 **[0094]** In order to separate several fluorophores in a dialysis liquid, it is also possible, besides the numerical analysis of the fluorescence spectrum as outlined above, using techniques to separate the sample into different fractions. This fractioning can be done, for example, by ultrafiltration of proteins which can be separated due to their high mass number from lower mass substances such as indoxyl sulfate. To achieve filtration, the dialysis solution which is going to be analyzed is fed through a filter with a suitable pore size. The filtrate and/or the concentrate can then be analyzed by irradiating it with light of the at least first wavelength and detecting the fluorescence light emitted by the respective fraction.

35 **[0095]** For the analysis of the dialysis liquid in the sample, it is contemplated analyzing it either in a separate branch of the dialysis apparatus, or by storing it in a separate volume, where it is treated and then feeding it again through the measurement cell 6.

40 **[0096]** Figure 6 shows schematically a layout of an apparatus which is arranged for carrying out the analysis on the used dialysis fluid separated from the main flow of the used dialysis fluid. To this end, a bypass conduit 13 is shown through which the larger portion of the used dialysis fluid passes. Accordingly, only a fraction of the flow of the used dialysis fluid output after having passed the membrane 3 flows through the cell 6.

45 **[0097]** Preferably, a valve 14 is present before the cell 6 such that samples can be separated from the constant flow of the used analyte. The separated flows can be analysed over a sufficiently long time such that also time resolved analysis on the identical sample can be carried out before it is discharged again. By means of the valve 14 it is also possible switching between a constant flow mode in the cell 6 when the valve 14 is always open, or a separated sample mode when the valve 14 is only opened to let some used dialysis fluid flow into the cell 6 and then close the valve as long as the respective sample is analysed in the cell 6.

50 **[0098]** A separation of different fractions of the sample can also be achieved in or before the cell 6 by means of electrophoresis, chromatography, filtering cascades, by using specific adsorbers or by marking specific substances or molecules by means of fluorescence active markers. A respective apparatus for carrying out the respective treatments on the sample before it is analysed in the cell 6 is schematically shown at reference numeral 15.

55 **[0099]** In a further preferred embodiment, the sample may be measured at least twice wherein the second measurement is carried out after the sample is physically and/or chemically treated. The actual treatment may be carried out by heating, by adding and/or removing reagents such as an acid, a chemical base or a salt, or by any other suitable treatment. The presence and/or concentration of a specific analyte is then determined taking into account the difference between the at least two measurements, namely the measurement before the treatment and the measurement after the treatment. The combination of the difference of the two fluorescence spectra and the fluorescence spectrum as such may provide additional information as to the respective analyte - or the composition of different analytes - in the dialysis liquid.

**[0100]** The respective apparatus for treating the sample is shown schematically in Figure 6 at reference numeral 16,

which may be a dosing apparatus for adding chemicals to the sample, and at reference numeral 17, which is an apparatus for physical treatment such as a heater.

[0101] As to the light source 7, it is also contemplated using, in a preferred embodiment, polarized light for exciting the dialysis liquid, in particular left-handed circularly polarized light and/or right-hand circularly polarized light.

5

## Claims

- 10 1. Method for monitoring a treatment of a patient, preferably for monitoring hemodialysis, hemodiafiltration and/or peritoneal dialysis, the method comprising the steps of:
- irradiating a sample of a liquid used in the treatment with irradiation light of at least a first irradiation wavelength;
  - detecting light emitted by the irradiated sample in at least a first detection wavelength wherein the detection wavelength is different from the first irradiation wavelength, and
  - 15 - determining the presence and/or concentration of at least one analyte in the sample on the basis of the detected light,
- characterized in that** the liquid is a dialysis liquid and the detected light includes fluorescence light and the presence and/or concentration of the at least one analyte in the sample is determined on the basis of the detected fluorescence light, wherein the irradiation light is UV-light having a wavelength of between 180 nm and 400 nm.
- 20 2. Method according to claim 1, wherein the presence and/or concentration of the analyte in the sample is determined on the basis of detected light of at least a first detection wavelength and a second detection wavelength, the first and second detection wavelengths being different from one another, and/or
- 25 wherein the presence and/or concentration of the analyte in the sample is determined on the basis of the spectrum of the detected light of the sample.
3. Method according to claim 1 or 2, wherein the irradiation light is UV-light having a wavelength between 250 nm and 300 nm, preferably light having a wavelength of 280 nm and/or 295 nm, and/or
- 30 wherein the sample is irradiated with irradiation light of at least two separated, distinct wavelengths, preferably at a wavelength of 280 nm and 295 nm.
4. Method according to any of the preceding claims, wherein the intensity of the irradiation light in the sample is determined and the determination of the presence and/or concentration of the analyte in the sample is compensated for the intensity of the irradiation light,
- 35 wherein preferably the absorption of the irradiation light in the sample is measured and the intensity of the irradiation light is determined on the basis of the measured absorption, wherein preferably the absorption in the sample is measured by means of a photo detector detecting the irradiation light transmitted through the sample and/or wherein Raman scattered light of the sample is obtained and the intensity of the irradiation light in the sample is determined
- 40 on the basis of the obtained Raman scattered light, and/or wherein preferably a Raman spectrum of the sample and/or the intensity at a water Raman peak of the Raman scattered light is obtained.
5. Method according to any of the preceding claims, wherein the detected light is detected in a time resolved manner, preferably wherein the irradiation light is pulsed.
- 45 6. Method according to any of the preceding claims, wherein the sample is irradiated with polarized irradiation light, preferably with left-handed circularly polarized irradiation light and/or right-handed circularly polarized irradiation light.
7. Method according to any of the preceding claims, wherein the light emitted by the sample is detected at least twice, wherein between the first and second detections the sample is treated physically and/or chemically and the presence and/or concentration of the analyte is determined taking into account the difference between the first and second detections, wherein the sample is preferably treated by heating, by adding and/or removing of reagents and/or by adding and/or removing of an acid, of a chemical base and/or of a salt.
- 50 8. Method according to any of the preceding claims, wherein the sample is separated from the flow of dialysis liquid for carrying out the determination of the presence and/or concentration of the analyte, or wherein the determination of the presence and/or concentration of the analyte is carried out continuously on the flow of dialysis liquid.
- 55

9. Method according to any of the preceding claims, wherein before irradiating the sample with the irradiation light, the sample is separated into different fractions, preferably by means of ultrafiltration, electrophoresis, chromatography, the addition of absorber and/or the addition of a fluorescent marker, and at least one of the fractions of the sample is irradiated with the irradiation light.

10. Method according to any one of the preceding claims, wherein the presence and/or concentration of at least two different analytes is determined on the basis of the detected light, wherein preferably after excitation at a specific irradiation wavelength the detected light is analysed as to the presence of the at least N different analytes by analyzing the detected light  $f(\lambda)$  to be given in the form of a linear superposition of the spectra of the N analytes:

$$f(\lambda) = \sum_{i=1}^N c_i s_i(\lambda)$$

$c_i$  being the unknown concentration of the  $i^{\text{th}}$  analyte and  $s_i(\lambda)$  being the known sensitivity of the  $i^{\text{th}}$  analyte as a function of the respective emission wavelength  $\lambda$ , wherein this equation is preferably solved for the unknown concentrations  $c_i$  by determining the spectrum at M different wavelengths  $\lambda_j$ , considering the above equation in the form of the following system of M equations with N unknowns:

$$\begin{pmatrix} f(\lambda_1) \\ f(\lambda_2) \\ \vdots \\ f(\lambda_M) \end{pmatrix} = \begin{pmatrix} s_1(\lambda_1) & s_2(\lambda_1) & \cdots & s_N(\lambda_1) \\ s_1(\lambda_2) & s_2(\lambda_2) & \cdots & s_N(\lambda_2) \\ \vdots & \vdots & \ddots & \vdots \\ s_1(\lambda_M) & s_2(\lambda_M) & \cdots & s_N(\lambda_M) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ \vdots \\ c_N \end{pmatrix}$$

and solving it numerically,

preferably by considering as the best solution for the above system of equations the one which provides, when being inserted into the above matrix, the superposition spectrum which has the lowest square deviation from the actually measured spectrum.

11. Apparatus for monitoring a treatment of a patient, preferably for monitoring hemodialysis, hemodiafiltration and/or peritoneal dialysis, the apparatus comprising:

- a light source (7) for irradiating a sample of a liquid used in the treatment with irradiation light of at least a first irradiation wavelength;
- a detector (9) for detecting light emitted by the irradiated sample in at least a first detection wavelength wherein the detection wavelength is different from the first irradiation wavelength; and
- a control and analysis unit (11) for determining the presence and/or concentration of at least one analyte in the sample on the basis of the detected light,

**characterized in that** the liquid is a dialysis liquid and the detector (9) is arranged to detect light including fluorescence light and the control and analysis unit (11) is arranged to determine the presence and/or concentration of the at least one analyte in the sample on the basis of the detected fluorescence light, wherein the light source emits irradiation light in the UV-range having a wavelength of between 180 nm and 400 nm.

12. Apparatus according to claim 11, wherein the light source emits irradiation light in the UV-range between 250 nm and 300 nm, preferably at 280 nm and/or 295 nm, and/or wherein the light source preferably is a AlInGaN diode, and/or wherein the light source is set to provide illumination light in at least two separated, distinct wavelengths, preferably at 280nm and 295nm.

13. Apparatus according to claim 11 or 12, wherein means for determining the intensity of the irradiation light in the sample are provided, wherein the means preferably comprise a photo detector (8) for determining the absorption

of the irradiation light in the sample of dialysis liquid and/or comprise means for obtaining a Raman spectrum and/or the intensity of the Raman scattered light at at least a specific wavelength.

14. Apparatus according to any one of claims 11 to 13, wherein means (16, 17) for treating the sample physically and/or chemically are present, preferably for treating the sample by heating, by adding and/or removing of reagents and/or by adding and/or removing of an acid, of a chemical base and/or of a salt and/or wherein means (15) for separating the sample into different fractions are given, preferably ultrafiltration, electrophoresis and/or chromatography equipment and/or means for adding an absorber and/or a fluorescent marker.
15. Apparatus according to any one of claims 11 to 14, wherein the control and analysis unit (11) is arranged to determine the presence and/or concentration of at least two different analytes on the basis of the detected light, wherein preferably the control and analysis unit (11) is arranged to analyze the detected light, after excitation at a specific irradiation wavelength, as to the presence of the at least N different analytes by analyzing the detected light  $f(\lambda)$  which is assumed to be given in the form of a linear superposition of the spectra of the N analytes:

$$f(\lambda) = \sum_{i=1}^N c_i s_i(\lambda)$$

$c_i$  being the unknown concentration of the  $i^{\text{th}}$  analyte and  $s_i(\lambda)$  being the known sensitivity of the  $i^{\text{th}}$  analyte as a function of the respective emission wavelength  $\lambda$ , wherein the control and analysis unit (11) is preferably arranged to solve this equation for the unknown concentrations  $c_i$  by determining the spectrum at M different wavelengths  $\lambda_j$ , considering the above equation in the form of the following system of M equations with N unknowns:

$$\begin{pmatrix} f(\lambda_1) \\ f(\lambda_2) \\ \vdots \\ f(\lambda_M) \end{pmatrix} = \begin{pmatrix} s_1(\lambda_1) & s_2(\lambda_1) & \cdots & s_N(\lambda_1) \\ s_1(\lambda_2) & s_2(\lambda_2) & \cdots & s_N(\lambda_2) \\ \vdots & \vdots & \ddots & \vdots \\ s_1(\lambda_M) & s_2(\lambda_M) & \cdots & s_N(\lambda_M) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ \vdots \\ c_N \end{pmatrix}$$

and solving it numerically, preferably by considering as the best solution for the above system of equations the one which provides, when being inserted into the above matrix, the superposition spectrum which has the lowest square deviation from the actually measured spectrum.

## Patentansprüche

1. Verfahren zum Überwachen einer Behandlung eines Patienten, bevorzugt zum Überwachen von Hämodialyse, Hämodiafiltration und/oder Peritonealdialyse, wobei das Verfahren die folgenden Schritte umfasst:

- Bestrahlen einer Probe einer in der Behandlung verwendeten Flüssigkeit mit einem Bestrahlungslicht bei zumindest einer ersten Bestrahlungswellenlänge;
- Detektieren von durch die bestrahlte Probe emittiertem Licht bei zumindest einer ersten Detektionswellenlänge, wobei die Detektionswellenlänge von der ersten Bestrahlungswellenlänge unterschiedlich ist, und
- Bestimmen des Vorhandenseins und/oder der Konzentration zumindest eines Analyten in der Probe basierend auf dem detektierten Licht,

### dadurch gekennzeichnet, dass

die Flüssigkeit eine Dialyseflüssigkeit ist und das detektierte Licht Fluoreszenzlicht aufweist, wobei das Vorhandensein und/oder die Konzentration des zumindest einen Analyten in der Probe basierend auf dem detektierten Fluoreszenzlicht bestimmt wird, wobei das Bestrahlungslicht UV-Licht mit einer Wellenlänge zwischen 180 nm und 400 nm ist.

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2. Verfahren gemäß Anspruch 1, wobei das Vorhandensein und/oder die Konzentration des Analyten in der Probe basierend auf detektiertem Licht zumindest einer ersten Detektionswellenlänge und einer zweiten Detektionswellenlänge bestimmt wird,  
wobei sich die erste und zweite Detektionswellenlänge voneinander unterscheiden und/oder wobei das Vorhandensein und/oder die Konzentration des Analyten in der Probe basierend auf dem Spektrum des detektierten Lichts der Probe bestimmt wird.
3. Verfahren gemäß Anspruch 1 oder 2, wobei das Bestrahlungslicht UV-Licht mit einer Wellenlänge zwischen 250 nm und 300 nm, bevorzugt Licht mit einer Wellenlänge von 280 nm und/oder 295 nm, ist, und/oder wobei die Probe mit Bestrahlungslicht bei zumindest zwei voneinander getrennten, unterschiedlichen Wellenlängen, bevorzugt mit Wellenlängen von 280 nm und 295 nm, bestrahlt wird.
4. Verfahren gemäß einem der vorherigen Ansprüche, wobei die Intensität des Bestrahlungslichts in der Probe bestimmt wird und das Bestimmen des Vorhandenseins und/oder der Konzentration des Analyten in der Probe für die Intensität des Bestrahlungslichts kompensiert wird,  
wobei bevorzugt die Absorption des Bestrahlungslichts in der Probe gemessen wird und die Intensität des Bestrahlungslichts basierend auf der gemessenen Absorption bestimmt wird,  
wobei bevorzugt die Absorption in der Probe mittels eines durch die Probe transmittierte Bestrahlungslicht detektierenden Photodetektors gemessen wird, und/oder  
wobei Raman-Streulicht der Probe erhalten wird und die Intensität des Bestrahlungslichts in der Probe basierend auf dem erhaltenen Raman-Streulicht bestimmt wird, und/oder  
wobei bevorzugt ein Raman-Spektrum der Probe und/oder die Intensität bei einem Raman-Maximum von Wasser des Raman-Streulichts erhalten wird.
5. Verfahren gemäß einem der vorherigen Ansprüche, wobei das detektierte Licht zeitaufgelöst detektiert wird, wobei das Bestrahlungslicht bevorzugt pulsiert ist.
6. Verfahren gemäß einem der vorherigen Ansprüche, wobei die Probe mit polarisiertem Bestrahlungslicht, bevorzugt mit linkszirkularem polarisiertem Bestrahlungslicht und/oder rechtszirkularem polarisiertem Bestrahlungslicht, bestrahlt wird.
7. Verfahren gemäß einem der vorherigen Ansprüche, wobei das durch die Probe emittierte Licht zumindest zwei Mal detektiert wird, wobei die Probe zwischen der ersten und zweiten Detektion physikalisch und/oder chemisch behandelt wird und das Vorhandensein und/oder die Konzentration des Analyten unter Einbeziehung der Differenz zwischen der ersten und zweiten Detektion bestimmt wird, wobei die Probe bevorzugt durch Erhitzen, durch Hinzufügen und/oder Entfernen eines Reagenz und/oder durch Hinzufügen und/oder Entfernen einer Säure, einer chemischen Base und/oder eines Salzes, behandelt wird.
8. Verfahren gemäß einem der vorherigen Ansprüche, wobei die Probe von dem Fluss von Dialyseflüssigkeit getrennt wird, um das Bestimmen des Vorhandenseins und/oder der Konzentration des Analyten auszuführen, oder wobei das Bestimmen des Vorhandenseins und/oder der Konzentration des Analyten kontinuierlich am Fluss von Dialyseflüssigkeit ausgeführt wird.
9. Verfahren gemäß einem der vorherigen Ansprüche, wobei die Probe vor dem Bestrahlen mit Bestrahlungslicht in unterschiedliche Fraktionen, bevorzugt mittels Ultrafiltration, Elektrophorese, Chromatographie, der Addition eines Absorbers und/oder der Addition eines fluoreszenten Markers, getrennt werden, und zumindest eine der Probefraktionen mit dem Bestrahlungslicht bestrahlt wird.
10. Verfahren gemäß einem der vorherigen Ansprüche, wobei das Vorhandensein und/oder die Konzentration von zumindest zwei unterschiedlichen Analyten basierend auf dem detektierten Licht bestimmt wird, wobei das detektierte Licht bevorzugt nach der Anregung bei einer spezifischen Bestrahlungswellenlänge bezüglich des Vorhandenseins von zumindest N unterschiedlichen Analyten analysiert wird durch Analysieren des detektierten Lichts  $f(\lambda)$ , welches in der Form einer linearen Superposition der Spektren der N Analyten gegeben ist:

$$f(\lambda) = \sum_{i=1}^N c_i s_i(\lambda)$$

wobei  $c_i$  die unbekannte Konzentration des  $i$ -ten Analyten und  $s_i(\lambda)$  die bekannte Sensitivität des  $i$ -ten Analyten als eine Funktion der jeweiligen Emissionswellenlänge  $\lambda$  ist, wobei die Gleichung bevorzugt nach den unbekanntem Konzentrationen  $c_i$  durch Bestimmen der Spektren bei  $M$  unterschiedlichen Wellenlängen  $\lambda_i$  gelöst wird, wobei die obere Gleichung in der Form des folgenden Systems von  $M$  Gleichungen mit  $N$  Unbekannten betrachtet wird:

$$\begin{pmatrix} f(\lambda_1) \\ f(\lambda_2) \\ \vdots \\ f(\lambda_M) \end{pmatrix} = \begin{pmatrix} s_1(\lambda_1) & s_2(\lambda_1) & \cdots & s_N(\lambda_1) \\ s_1(\lambda_2) & s_2(\lambda_2) & \cdots & s_N(\lambda_2) \\ \vdots & \vdots & \ddots & \vdots \\ s_1(\lambda_M) & s_2(\lambda_M) & \cdots & s_N(\lambda_M) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ \vdots \\ c_N \end{pmatrix}$$

und numerisch gelöst wird,

wobei bevorzugt die Lösung, welche, wenn in der oberen Matrix eingefügt, das Superpositionsspektrum mit der von dem tatsächlich gemessenen Spektrum niedrigsten quadratischen Abweichung bereitstellt, als beste Lösung für das obere System der Gleichungen betrachtet wird.

11. Vorrichtung zum Überwachen einer Behandlung eines Patienten, bevorzugt zum Überwachen von Hämodialyse, Hämodiafiltration und/oder Peritonealdialyse, wobei die Vorrichtung umfasst:

- eine Lichtquelle (7) zum Bestrahlen einer Probe einer in der Behandlung verwendeten Flüssigkeit mit einem Bestrahlungslicht bei zumindest einer ersten Bestrahlungswellenlänge;
- einen Detektor (9) zum Detektieren von durch die bestrahlte Probe emittiertem Licht bei zumindest einer ersten Detektionswellenlänge, wobei sich die Detektionswellenlänge von der ersten Bestrahlungswellenlänge unterscheidet, und
- eine Steuer-/Regelungs- und Analyseeinheit (11) zum Bestimmen des Vorhandenseins und/oder der Konzentration zumindest eines Analyten in der Probe basierend auf dem detektierten Licht,

**dadurch gekennzeichnet, dass**

die Flüssigkeit eine Dialyseflüssigkeit ist und der Detektor (9) so angeordnet ist, dass er Fluoreszenzlicht aufweisendes Licht detektiert, und wobei die Steuer-/Regelungs- und Analyseeinheit (11) so angeordnet ist, dass sie das Vorhandensein und/oder die Konzentration des zumindest einen Analyten in der Probe basierend auf dem detektierten Licht bestimmt, wobei die Lichtquelle Bestrahlungslicht im UV-Bereich mit einer Wellenlänge zwischen 180 nm und 400 nm emittiert.

12. Vorrichtung gemäß Anspruch 11, wobei die Lichtquelle Bestrahlungslicht im UV-Bereich mit einer Wellenlänge zwischen 250 nm und 300 nm, bevorzugt von 280 nm und/oder 295 nm, emittiert, und/oder wobei die Lichtquelle bevorzugt eine AlInGaN Diode ist, und/oder wobei die Lichtquelle eingestellt ist, um Bestrahlungslicht mit zumindest zwei getrennten, unterschiedlichen Wellenlängen, bevorzugt mit einer Wellenlänge von 280 nm und 295 nm, bereitzustellen.
13. Vorrichtung gemäß Anspruch 11 oder 12, wobei Mittel zum Bestimmen der Intensität des Bestrahlungslichts in der Probe bereitgestellt sind, wobei die Mittel bevorzugt einen Photodetektor (8) zum Bestimmen der Absorption des Bestrahlungslichts in der Dialyseflüssigkeitsprobe und/oder Mittel zum Erhalten eines Raman-Spektrums und/oder der Intensität des Raman-Streulichts für zumindest eine spezifische Wellenlänge umfassen.
14. Vorrichtung gemäß einem der Ansprüche 11 bis 13, wobei Mittel (16, 17) zum physikalischen und/oder chemischen Behandeln der Probe vorhanden sind, bevorzugt zum Behandeln der Probe durch Erhitzen, durch Hinzufügen und/oder Entfernen von Reagenzien und/oder durch Hinzufügen und/oder Entfernen einer Säure, einer chemischen Base und/oder eines Salzes, und/oder wobei Mittel (15) zum Auftrennen der Probe in unterschiedliche Fraktionen

bereitgestellt sind, bevorzugt eine Ultrafiltrations-, Elektrophorese- und/oder Chromatographieanlage, und/oder Mittel zur Addition eines Absorbers und/oder eines fluoreszenten Markers.

- 5 15. Vorrichtung gemäß einem der Ansprüche 11 bis 14, wobei die Steuer-/Regelungs- und Analyseeinheit (11) angeordnet ist, um das Vorhandensein und/oder die Konzentration von zumindest zwei unterschiedlichen Analyten basierend auf dem detektierten Licht zu bestimmen, wobei bevorzugt die Steuer-/Regelungs- und Analyseeinheit (11) angeordnet ist, um das detektierte Licht nach Anregung bei einer spezifischen Bestrahlungswellenlänge bezüglich des Vorhandenseins von zumindest N unterschiedlichen Analyten zu analysieren durch Analysieren des detektierten Lichts  $f(\lambda)$ , welches in der Form einer linearen Superposition der Spektren der N Analyten als gegeben angenommen ist:

$$f(\lambda) = \sum_{i=1}^N c_i s_i(\lambda)$$

wobei  $c_i$  die unbekannte Konzentration des i-ten Analyten und  $s_i(\lambda)$  die bekannte Sensitivität des i-ten Analyten als eine Funktion der jeweiligen Emissionswellenlänge  $\lambda$  ist, wobei die Steuer-/Regelungs- und Analyseeinheit (11) bevorzugt angeordnet ist, um die Gleichung nach den unbekannt Konzentrationen  $c_i$  durch Bestimmen der Spektren bei M unterschiedlichen Wellenlängen  $\lambda_i$  zu lösen, wobei die obere Gleichung in der Form des folgenden Systems von M Gleichungen mit N Unbekannten betrachtet wird:

$$\begin{pmatrix} f(\lambda_1) \\ f(\lambda_2) \\ \vdots \\ f(\lambda_M) \end{pmatrix} = \begin{pmatrix} s_1(\lambda_1) & s_2(\lambda_1) & \cdots & s_N(\lambda_1) \\ s_1(\lambda_2) & s_2(\lambda_2) & \cdots & s_N(\lambda_2) \\ \vdots & \vdots & \ddots & \vdots \\ s_1(\lambda_M) & s_2(\lambda_M) & \cdots & s_N(\lambda_M) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ \vdots \\ c_N \end{pmatrix}$$

und numerisch gelöst wird,

wobei bevorzugt die Lösung, welche, wenn in der oberen Matrix eingefügt, das Superpositionsspektrum mit der von dem tatsächlich gemessenen Spektrum niedrigsten quadratischen Abweichung bereitstellt, als beste Lösung für das obere System der Gleichungen betrachtet wird.

## Revendications

- 40 1. Procédé de surveillance d'un traitement d'un patient, de préférence de surveillance d'une hémodialyse, d'une hémodiafiltration et/ou d'une dialyse péritonéale, le procédé comprenant les étapes suivantes :

- irradier un échantillon d'un liquide utilisé dans le traitement avec une lumière d'irradiation d'au moins une première longueur d'onde d'irradiation ;
- 45 - détecter la lumière émise par l'échantillon irradié dans au moins une première longueur d'onde de détection, où la longueur d'onde de détection est différente de la première longueur d'onde d'irradiation ; et
- déterminer la présence et/ou la concentration d'au moins un analyte dans l'échantillon sur la base de la lumière détectée,

50 **caractérisé en ce que** le liquide est un liquide de dialyse et la lumière détectée comprend une lumière fluorescente, et la présence et/ou la concentration de l'au moins un analyte dans l'échantillon sont déterminées sur la base de la lumière fluorescente détectée, où la lumière d'irradiation est une lumière UV ayant une longueur d'onde comprise entre 180 nm et 400 nm.

- 55 2. Procédé selon la revendication 1, dans lequel la présence et/ou la concentration de l'analyte dans l'échantillon sont déterminées sur la base de la lumière détectée d'au moins une première longueur d'onde de détection et une seconde longueur d'onde de détection, les première et seconde longueurs d'onde de détection étant différent l'une des l'autre, et/ou

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dans lequel la présence et/ou la concentration de l'analyte dans l'échantillon sont déterminées sur la base du spectre de la lumière détectée de l'échantillon.

- 5
3. Procédé selon la revendication 1 ou la revendication 2, dans lequel la lumière d'irradiation est une lumière UV ayant une longueur d'onde comprise entre 250 nm et 300 nm, de préférence une lumière ayant une longueur d'onde de 280 nm et/ou 295 nm, et/ou dans lequel l'échantillon est irradié avec une lumière d'irradiation d'au moins deux longueurs d'onde séparées, distinctes, de préférence à des longueurs d'onde de 280 nm et 295 nm.
- 10
4. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'intensité de la lumière d'irradiation dans l'échantillon est déterminée, et la détermination de la présence et/ou de la concentration de l'analyte dans l'échantillon est compensée par rapport à l'intensité de la lumière d'irradiation, dans lequel, de préférence, l'absorption de la lumière d'irradiation dans l'échantillon est mesurée et l'intensité de la lumière d'irradiation est déterminée sur la base de l'absorption mesurée, dans lequel, de préférence, l'absorption dans l'échantillon est mesurée au moyen d'un photodétecteur détectant la lumière d'irradiation transmise à travers l'échantillon et/ou dans lequel la lumière diffusée par effet Raman de l'échantillon est obtenue et l'intensité de la lumière d'irradiation dans l'échantillon est déterminée sur la base de la lumière diffusée par effet Raman obtenue, et/ou dans lequel, de préférence, un spectre Raman de l'échantillon et/ou l'intensité à un pic Raman de l'eau de la lumière diffusée par effet Raman est obtenu.
- 15
5. Procédé selon l'une quelconque des revendications précédentes, dans lequel la lumière détectée est détectée de manière résolue dans le temps, de préférence dans lequel la lumière d'irradiation est pulsée.
- 20
6. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'échantillon est irradié avec une lumière d'irradiation polarisée, de préférence avec une lumière d'irradiation à polarisation circulaire à gauche et/ou une lumière d'irradiation à polarisation circulaire à droite.
- 25
7. Procédé selon l'une quelconque des revendications précédentes, dans lequel la lumière émise par l'échantillon est détectée au moins deux fois, où, entre les première et seconde détections, l'échantillon est traité physiquement et/ou chimiquement, et la présence et/ou la concentration de l'analyte sont déterminées en tenant compte de la différence entre les première et seconde détections, où l'échantillon est de préférence traité par chauffage, en ajoutant et/ou en enlevant des réactifs et/ou en ajoutant et/ou en enlevant un acide, une base chimique et/ou un sel.
- 30
8. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'échantillon est séparé du débit de liquide de dialyse pour procéder à la détermination de la présence et/ou de la concentration de l'analyte, ou dans lequel la détermination de la présence et/ou de la concentration de l'analyte est effectuée de manière continue sur le débit de liquide de dialyse.
- 35
9. Procédé selon l'une quelconque des revendications précédentes, dans lequel, avant l'irradiation de l'échantillon avec la lumière d'irradiation, l'échantillon est séparé en différentes fractions, de préférence par ultrafiltration, électrophorèse, chromatographie, ajout d'absorbant et/ou ajout d'un marqueur fluorescent, et au moins une des fractions de l'échantillon est irradiée avec la lumière d'irradiation.
- 40
10. Procédé selon l'une quelconque des revendications précédentes, dans lequel la présence et/ou la concentration d'au moins deux analytes différents sont déterminées sur la base de la lumière détectée, dans lequel, de préférence, après excitation à une longueur d'onde d'irradiation spécifique, la lumière détectée est analysée quant à la présence des au moins N différents analytes par analyse de la lumière détectée  $f(\lambda)$  fourni sous la forme d'une superposition linéaire des spectres des N analytes :
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- 50

$$f(\lambda) = \sum_{i=1}^N c_i s_i(\lambda)$$

55

$c_i$  étant la concentration inconnue du  $i^{\text{ème}}$  analyte et  $s_i(\lambda)$  étant la sensibilité connue du  $i^{\text{ème}}$  analyte, comme fonction

de la longueur d'onde d'émission respective  $\lambda$ , où cette équation est de préférence résolue pour les concentrations inconnues  $c_i$  en déterminant le spectre à M longueurs d'ondes différentes  $\lambda_j$ , compte tenu de l'équation ci-dessus sous la forme du système suivant de M équations à N inconnues :

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$$\begin{pmatrix} f(\lambda_1) \\ f(\lambda_2) \\ \vdots \\ f(\lambda_M) \end{pmatrix} = \begin{pmatrix} s_1(\lambda_1) & s_2(\lambda_1) & \cdots & s_N(\lambda_1) \\ s_1(\lambda_2) & s_2(\lambda_2) & \cdots & s_N(\lambda_2) \\ \vdots & \vdots & \ddots & \vdots \\ s_1(\lambda_M) & s_2(\lambda_M) & \cdots & s_N(\lambda_M) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ \vdots \\ c_N \end{pmatrix}$$

et en la résolvant numériquement,

de préférence en considérant comme la meilleure solution pour le système d'équations ci-dessus celle qui fournit, lorsqu'elle est insérée dans la matrice ci-dessus, le spectre de superposition qui a le plus faible écart quadratique par rapport au spectre réellement mesuré.

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11. Appareil de surveillance d'un traitement d'un patient, de préférence de surveillance d'une hémodialyse, d'une hémofiltration et/ou d'une dialyse péritonéale, l'appareil comprenant :

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- une source de lumière (7) pour irradier un échantillon d'un liquide utilisé dans le traitement avec une lumière d'irradiation d'au moins une première longueur d'onde d'irradiation ;
- un détecteur (9) pour détecter la lumière émise par l'échantillon irradié dans au moins une première longueur d'onde de détection, où la longueur d'onde de détection est différente de la première longueur d'onde d'irradiation ; et
- une unité de contrôle et d'analyse (11) pour déterminer la présence et/ou la concentration d'au moins un analyte dans l'échantillon sur la base de la lumière détectée,

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**caractérisé en ce que** le liquide est un liquide de dialyse et le détecteur (9) est agencé pour détecter une lumière comprenant une lumière fluorescente et l'unité de contrôle et d'analyse (11) est agencée pour déterminer la présence et/ou la concentration de l'au moins un analyte dans l'échantillon sur la base de la lumière fluorescente détectée, où la source de lumière émet une lumière d'irradiation dans la gamme des UV ayant une longueur d'onde comprise entre 180 nm et 400 nm.

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12. Appareil selon la revendication 11, dans lequel la source de lumière émet une lumière d'irradiation dans la gamme des UV entre 250 nm et 300 nm, de préférence à 280 nm et/ou 295 nm, et/ou dans lequel la source de lumière est de préférence une diode AlInGaN, et/ou dans lequel la source de lumière est réglée pour fournir une lumière d'irradiation à au moins deux longueurs d'onde séparées, distinctes, de préférence à 280 nm et 295 nm.

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13. Appareil selon la revendication 11 ou la revendication 12, dans lequel des moyens pour déterminer l'intensité de la lumière d'irradiation dans l'échantillon sont fournis, dans lequel les moyens comprennent de préférence un photodétecteur (8) pour déterminer l'absorption de la lumière d'irradiation dans l'échantillon de liquide de dialyse et/ou comprennent des moyens pour obtenir un spectre de Raman et/ou l'intensité de la lumière diffusée par effet Raman à au moins une longueur d'onde spécifique.

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14. Appareil selon l'une quelconque des revendications 11 à 13, dans lequel des moyens (16, 17) pour traiter l'échantillon physiquement et/ou chimiquement sont présents, de préférence pour traiter l'échantillon par chauffage, en ajoutant et/ou en enlevant des réactifs et/ou en ajoutant et/ou en enlevant un acide, une base chimique et/ou un sel, et/ou dans lequel des moyens (15) pour séparer l'échantillon en différentes fractions sont proposés, de préférence un équipement d'ultrafiltration, d'électrophorèse et/ou de chromatographie et/ou des moyens pour ajouter un absorbeur et/ou un marqueur fluorescent.

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15. Appareil selon l'une quelconque des revendications 11 à 14, dans lequel l'unité de contrôle et d'analyse (11) est agencée pour déterminer la présence et/ou la concentration d'au moins deux analytes différents sur la base de la lumière détectée,

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dans lequel, de préférence, l'unité de contrôle et d'analyse (11) est agencée pour analyser la lumière détectée, après excitation à une longueur d'onde d'irradiation spécifique, quant à la présence des au moins N différents analytes par analyse de la lumière détectée  $f(\lambda)$  qui est supposée être fourni sous la forme d'une superposition

linéaire des spectres des N analytes :

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$$f(\lambda) = \sum_{i=1}^N c_i s_i(\lambda)$$

10

$c_i$  étant la concentration inconnue du  $i^{\text{ème}}$  analyte et  $s_i(\lambda)$  étant la sensibilité connue du  $i^{\text{ème}}$  analyte, comme fonction de la longueur d'onde d'émission respective  $\lambda$ , où l'unité de contrôle et d'analyse (11) est de préférence agencée pour résoudre cette équation pour les concentrations inconnues  $c_i$  en déterminant le spectre à M longueurs d'ondes différentes  $\lambda_j$ , compte tenu de l'équation ci-dessus sous la forme du système suivant de M équations à N inconnues :

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$$\begin{pmatrix} f(\lambda_1) \\ f(\lambda_2) \\ \vdots \\ f(\lambda_M) \end{pmatrix} = \begin{pmatrix} s_1(\lambda_1) & s_2(\lambda_1) & \cdots & s_N(\lambda_1) \\ s_1(\lambda_2) & s_2(\lambda_2) & \cdots & s_N(\lambda_2) \\ \vdots & \vdots & \ddots & \vdots \\ s_1(\lambda_M) & s_2(\lambda_M) & \cdots & s_N(\lambda_M) \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ \vdots \\ c_N \end{pmatrix}$$

20

et en la résolvant numériquement, de préférence en considérant comme la meilleure solution pour le système d'équations ci-dessus celle qui fournit, lorsqu'elle est insérée dans la matrice ci-dessus, le spectre de superposition qui a le plus faible écart quadratique par rapport au spectre réellement mesuré.

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Fig. 1

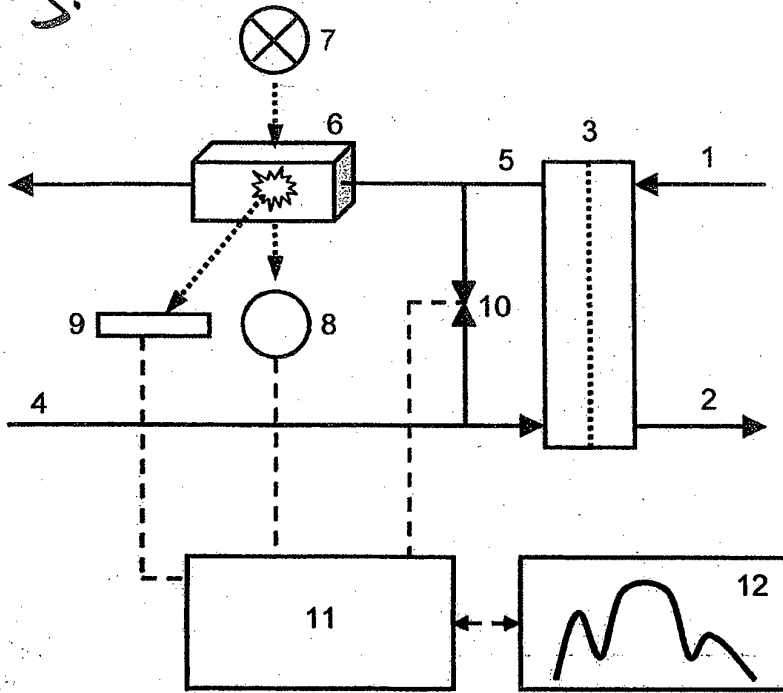


Fig. 2

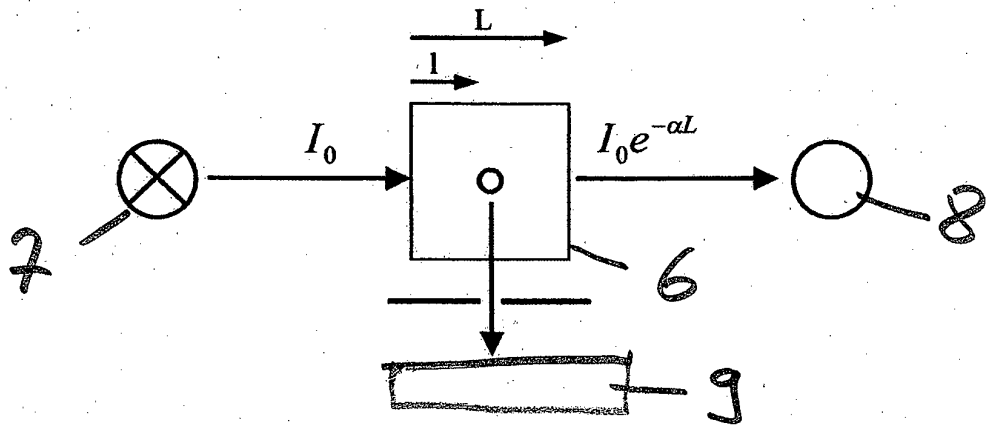


Fig. 3

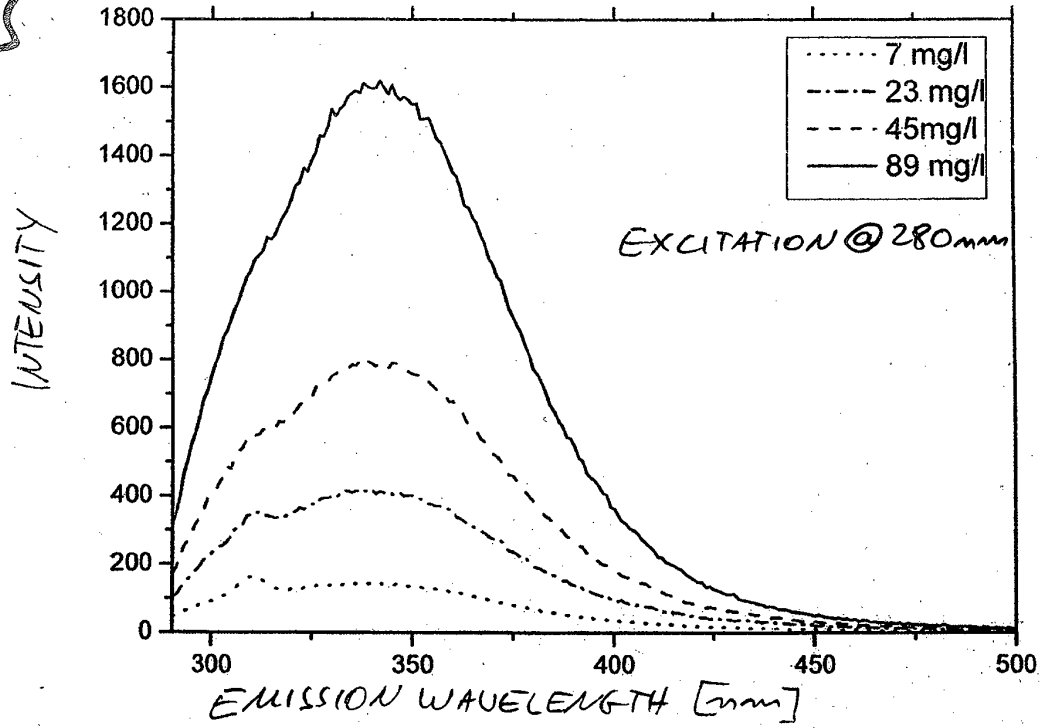


Fig. 4

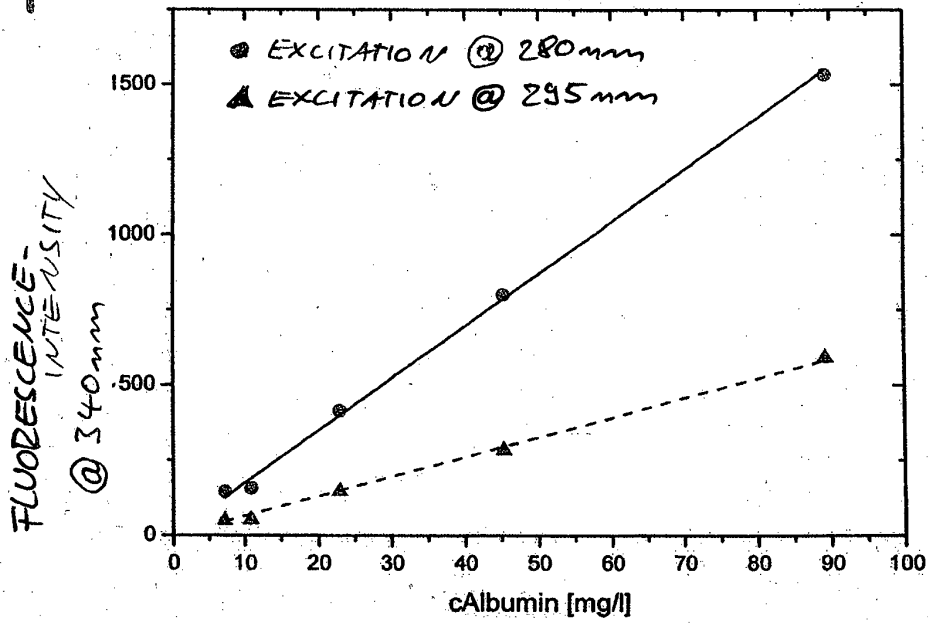


Fig 5

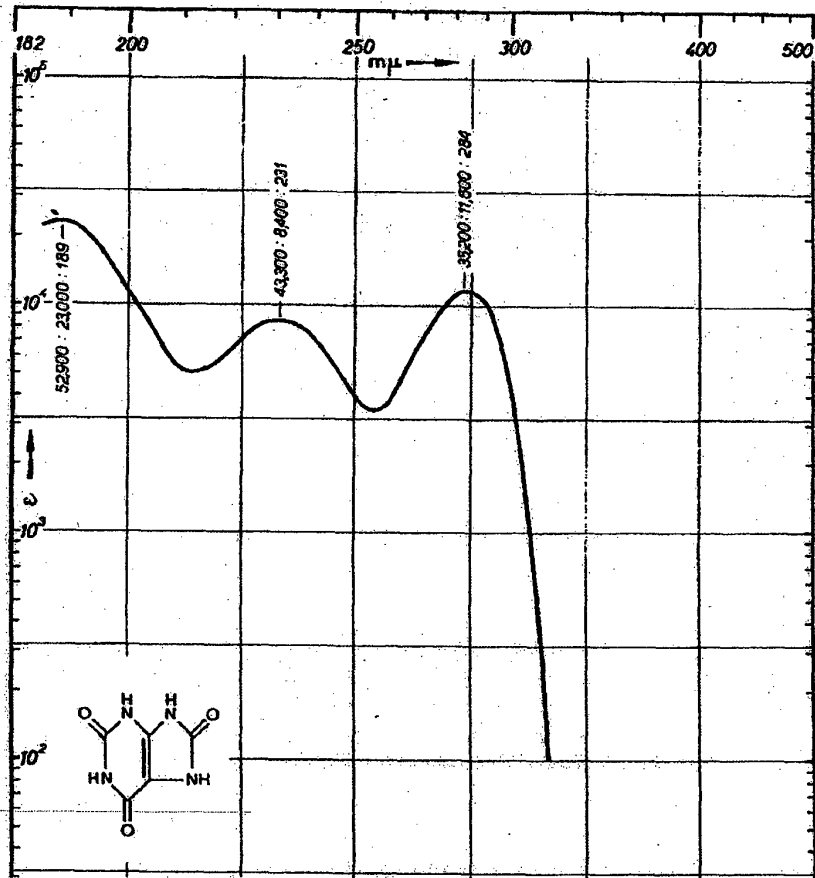
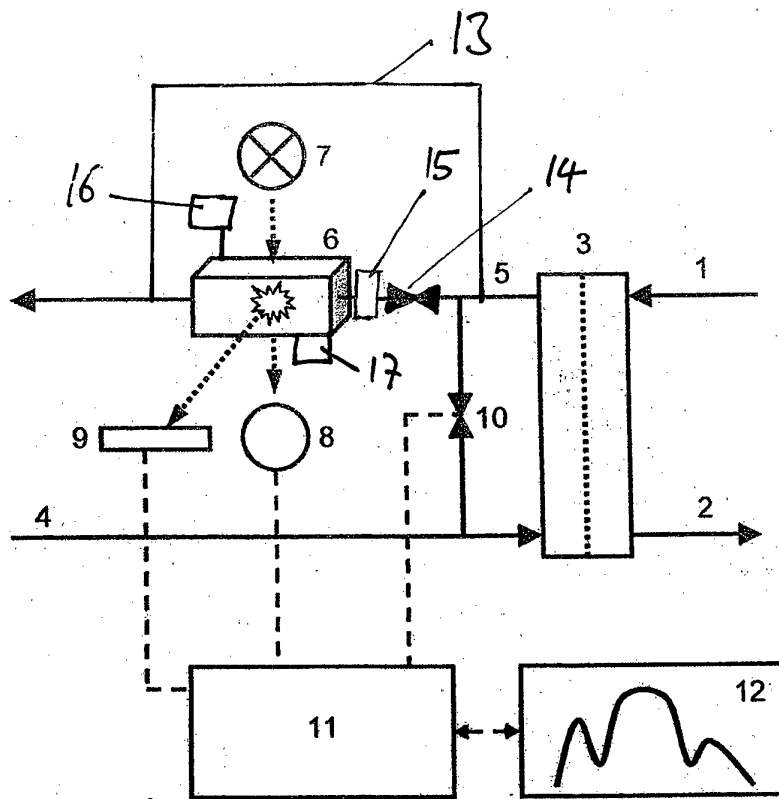


Fig. 6



**REFERENCES CITED IN THE DESCRIPTION**

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专利名称(译)	用于监测患者治疗的方法和装置，优选用于监测血液透析，血液透析滤过和/或腹膜透析		
公开(公告)号	<a href="#">EP2510958B1</a>	公开(公告)日	2015-07-22
申请号	EP2011161916	申请日	2011-04-11
[标]申请(专利权)人(译)	弗雷森纽斯医疗护理德国有限责任公司		
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发明人	GROSS, MALTE KOPPERSCHMIDT, PASCAL MAIERHOFER, ANDREAS GAGEL, ALFRED		
IPC分类号	A61M1/36 A61B5/00		
CPC分类号	A61B5/14546 A61B5/1455 A61M1/367 A61B5/14557 A61B5/0071 A61B5/0075 A61B5/0082 G01N21/6486 G01N21/65		
其他公开文献	EP2510958A1		
外部链接	<a href="#">Espacenet</a>		

摘要(译)

本发明涉及一种用于监测患者治疗的方法，优选用于监测血液透析，血液透析滤过和/或腹膜透析，该方法包括以下步骤：用至少一种照射光照射治疗中使用的透析液样品。第一照射波长，检测由照射样品以至少第一检测波长发射的光，检测波长不同于第一照射波长，并且基于样品确定样品中至少一种分析物的存在和/或浓度检测到的光线。

$$f(\lambda) = \sum_{i=1}^N c_i s_i(\lambda)$$