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Review

A review on creatinine measurement techniques

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ABSTRACT

This paper reviews the entire recent global tendency for creatinine measurement. Creatinine biosensors involve complex relationships between biology and micro-mechatronics to which the blood is subjected. Comparison between new and old methods shows that new techniques (e.g. Molecular Imprinted Polymers based algorithms) are better than old methods (e.g. Elisa) in terms of stability and linear range. All methods and their details for serum, plasma, urine and blood samples are surveyed. They are categorized into five main algorithms: optical, electrochemical, impedometrical, Ion Selective Field-Effect Transistor (ISFET) based technique and chromatography. Response time, detection limit, linear range and selectivity of reported sensors are discussed. Potentiometric measurement technique has the lowest response time of 4–10 s and the lowest detection limit of 0.28 nmol L^{-1} belongs to chromatographic technique. Comparison between various techniques of measurements indicates that the best selectivity belongs to MIP based and chromatographic techniques.

Contents

1. Introduction

One of the components of human blood is creatinine (2-amino-1-methyl-2-imidazoline-4-one). It is the final product of creatine metabolism in mammals [1] which is done in skeletal muscles to release energy [2]. Creatinine is extracted from the

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body by renal excretion at a relatively constant rate [1]. Kidney problems, thyroid malfunction and muscular disorders increase creatinine concentration in blood serum, therefore measuring creatinine concentration in blood or serum leads to diagnose those disorders [3]. Recently, there has been a great leap towards manufacturing simple, accurate and reliable biosensors to measure the amount of creatinine [1–4]. The normal clinical range for creatinine is 44–106 μmol L^{-1} [5], however it can be less or more according to age and gender [6]. In kidney malfunction, creatinine concentration can exceed 1000 mmol L^{-1}. Values more than 140 mmol L^{-1} mean needing for more clinical assays and more than 530 mmol L^{-1} is a sign of having kidney disease [5]. Patients suffering from kidney disease need a device to control creatinine concentration in blood daily [7]. Hence studying the characteristics of all sensors will be very helpful for its control.

Biosensors reviewed in this paper are used for creatinine measurement in serum, plasma, urine and blood samples. Table 1 shows some of these biosensors. Fig. 1 is a block diagram of a typical biosensor; two main subsystems of a biosensor are receptor and transducer. The receptor detects the target molecules. Usual receptors are antibodies, enzymes, cells, Molecular Imprinted Polymers (MIPs) and plant or animal tissues [14]. The transducer detects the interaction between receptor and bioanalyte. Usual techniques for transduction are optical, electrical, electrochemical, mass based and temperature based methods.

In this paper all types of creatinine sensors and their transduction methods are reviewed. Transduction methods can be classified in optical, electrochemical, impedometric, Ion Selective Field-Effect Transistor (ISFET) based and chromatographic methods. Most common method for creatinine detection is spectrophotometry which is one of the optical methods. But some materials interfere in result. Hence other methods with less interference can be useful. This factor is called selectivity [15]. For example Spierto et al. [16] showed that chromatographic method for creatinine measurement has less interference in comparison with optical method. Problem of selectivity was a reason for using membranes like MIP which are able to select just creatinine molecules. Panasyuk-Delaney et al. [15] claimed that using MIP in capacitive creatinine biosensor causes to achieve high selectivity in result. The other factor for comparing measurement methods can be response time. For example Fossati et al. [17] developed an optical sensor in which the response time is 30 min whereas the response time of sensor which is developed by Panasyuk-Delaney et al. [15] is 2 min. Third factor is linear range of detection. Appropriate linear range for a biosensor should be between the normal value of creatinine in blood up to the value that is a higher amount in kidney failure. Walsh and Dempsey [18] implemented a chromatography based biosensor for creatinine with linear range 0–4.4 mmol L^{-1}. It is a wide linear range for creatinine measurement according to the amounts declared above for normal and abnormal amount of creatinine in blood. Lifetime is forth factor for selecting biosensor. It is obvious that biosensor with long lifetime is more useful. For example in enzyme based biosensors, lifetime of an enzyme depends on immobilization strategy [19]. Therefore immobilization methods for enzymes should be investigated too.

The rest of paper is organized as follows. Common receptors for creatinine biosensors are described in Section 2. In Section 3, five mentioned methods as well as transducers for creatinine measurement are described. In each subsection, the details of measured creatinine concentration will be reported in mol L^{-1} or g L^{-1} (1 mmol L^{-1}) which is equal to 0.113 g L^{-1} [20]. Section 4 is about glomerular filtration and creatinine clearance and finally Section 5 concludes the paper.

Table 1
Creatinine biosensors which are used for serum, plasma, urine and whole blood.

Sample type	Refs.
Serum	[9,12,22,38,73,85,91,92,104]
Plasma	[4,9,22,64,90]
Urine	[3,9–13]
Whole blood	[8,64,81]

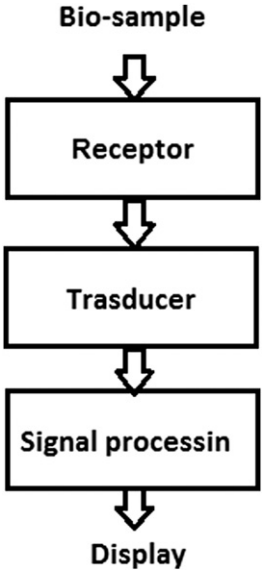

Fig. 1. Block diagram of a typical biosensor.

2. Receptors of creatinine biosensors

2.1. Enzyme

Enzymes change creatinine into other measurable materials (NH_4^+ or H_2O_2). Transducers for NH_4^+ (pH detector electrode) and H_2O_2 (oxygen detector electrode) were developed before, and their concentration is relevant to the serum creatinine concentration. Enzymes which are used in creatinine sensors are shown in Fig. 4.

Using sequential enzymes is highly selective for detection of creatinine; however, the cost of this method is high [7]. The Lifetime of an enzyme based sensor is limited by enzyme activity [21]. Enzyme based and Jaffe based sensors are used widely in laboratories [22]. Enzymes can be used with optical, Electrochemical and ISFET based transducers as a receptor. As declared before, immobilization method can effect on sensor lifetime [16], hence it will discussed in next subsection.

2.1.1. Immobilization

Usual methods for enzyme immobilization are gel entrapment, polymer entrapment, crosslinking, direct nonimmobilized deposition [5], adsorption, Covalent binding and Encapsulation [23]. Among these, using crosslinking improves stability but causes the sensitivity and the analytical range to decrease [5]. Using polymer entrapment is usual too. Some immobilization ways in creatinine sensors are entrapment in Poly (1, 2-diaminobenzene) [24], coimmobilization in a hydrogel network based on Poly Vinyl Alcohol (PVA) [25], crosslinking by glutaraldehyde [26,27] and entrapment on a ferrocene embedded carbon paste electrode [28]. In both potentiometric and amperometric transducers, the

immobilization way will be mentioned. Enzyme entrapped polymer layers can be categorized in three states [24]:

1. Conducting polymer: Some polymers are conductive like ones which are electrosynthesized from pyrrole, N-methylpyrrole and aniline. These polymers can immobilize the enzyme and provide electrical wiring of the enzyme simultaneously.
2. Non-conducting polymer: This membrane with "built-in permselectivity" can immobilize the enzyme and reject electroactive interferents as well as fouling species.
3. Multilayer membranes: These membranes are used for biosensors which have multi enzyme construction. Furthermore, they can be used as a mono layer membrane to reject interferences, improve stability and have linear response.

2.2. MIP

MIP is used as an artificial receptor in bioanalytes. It is accepted as a tool for receptor mimicking recognition sites [29]. To build MIP, a mixture of monomer, crosslinker and template molecules are used. Crosslinker links the monomer molecules to construct an integrated chain of polymer. Template molecules have special shape and by removing them from polymer. There will be some special shape holes in which target molecules in blood or urine samples can be placed. Selecting a proper crosslinker prevents constructing wrong cavities [14]. Hence, other molecules cannot place there and affect the results. The approach called "Bite-and-Switch" is combined with molecular imprinting to select proper materials for creatine and creatinine detection [30]. This approach creates higher crosslinking for MIP by imprinting polymer with methylated analogs of the template. Grafting photo-polymerization, forms highly crosslinked molecularly imprinted polymers with high sensitivity, and stability [31]. One of problems with MIPs is the lack of ability for removing the template from them completely [14].

Advantages of MIPs are high selectivity, sensitivity and stability [31]. They have high physical and chemical stability towards various external degrading factors, solvents, metal ions, and acid treatments. Also the duration of synthesis is less in comparison with other sensors [14]. Some kinds of monomer and crosslink agents are used to configure MIPs for creatinine detection. For example: 2-Acrylamido-2-methy l-1-propanesulfonic acid (AMPS) as a monomer and N, N-methylenediacrylamide (MBA) as crosslinker [15], poly ethylene-co-vinyl-alcohol (EVAL) and 4-vinylpyridine (4-Vpy) as monomer and divinylbenzene as crosslinker [32–36]. Other examples are: melamine (mel) and chloranil (chl) with low_level crosslinking network [37] and β-cyclodextrin (β-CD) as monomers and epichlorohydrin (EPI) as crosslinkers [38]. In addition, polymethacrylic acid is crosslinking by ethylene glycol diglycidyl ether [2]. MIP as a receptor can be used by chromatographic, ISFET based, capacitive and electrochemical sensors.

2.3. Antibody

Antibody (as a receptor) is used for creatinine measurement in amperometric sensors. Mechanism of detection and measurement will be described in amperometric sensors section.

3. Transducers of creatinine biosensors

In transducer parts of creatinine sensors optical, chemical, physical and electrical properties of materials are used. They will be discussed below.

3.1. Optical transducers

The most popular method for creatinine measurement is optical sensing. It is categorized into two main groups: Light diffraction and Spectrophotometry.

3.1.1. Light diffraction

In this method, composite hydrogel layers are used. They are photonic crystals in which the embedded Crystalline Colloidal Array (CCA) diffracts visible light and appears intensely colored. Volume phase transition of the hydrogel layer causes changing in the CCA lattice spacing, which changes the diffracted wavelength of light. Creatinine within the gel is rapidly hydrolyzed by the Creatinase enzyme (it will be introduced in Amperometric sensors). It releases OH^- which red shifts the composite diffraction. Linear range of these sensors is 0.01–0.7 mmol L^{-1}, and their detection limit is 6 μmol L^{-1} [7].

3.1.2. Spectrophotometry

In the Spectrophotometry method absorption of light with special wave length is measured. The amount of absorbance is related to the target concentration in the sample. Fig. 2 indicates schematic of this method. In sensors which use spectrophotometry a chemical reaction called Jaffe is done [9,39]; this reaction changes creatinine into an orange complex and it is measured by spectrophotometry.

alkaline picrate + creatinine → orange complex

This reaction was done, firstly, by Jaffe in 1886 [40]. There are some other materials (e.g. dinitrobenzoic acid) [9,40] which convert creatinine into a colorful complex, but alkaline picrate is more stable and causes grater light absorption [9]. This method may have few problems; some species in blood such as sugars, urea, uric acid, pyruvate, dopamine [7], acetone, acetoacetic acid, fructose, glucose [40], Ascorbate, cefoxitin, cephalotin, cefatril and cefazolin [41] interfere with this technique. Temperature and pH can affect the results too [40]. The maximum absorption for this method is reported for 485 nm [40] and 420–550 nm [10]. Table 2 shows some results of spectrophotometric sensors. This method is time-consuming and could not be selective regarding to interference of other materials [42]. Another way for creatinine measurement is the diffusion reflectance UV (DR-UV) spectroscopy. In this method, the target molecules are concentrated on a specific solid adsorbent like in the Solid Phase Extraction (SPE) procedure, then a UV spectrum is taken, and the measurement is followed like spectrophotometry [43].

3.1.3. Colorimetry

Colorimetric method is like spectrophotometry but the used wave length is in visible range of the electromagnetic spectrum. In this method two chemical reactions are used for measurement.

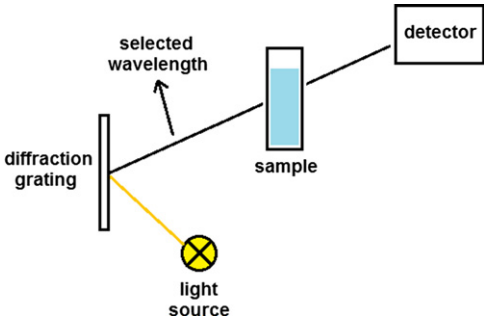

Fig. 2. Schematic of spectrophotometry.

Jaffe reaction [44,45,46,47] and sequence of three enzymatic reactions showed in Fig. 4 [17,48,49]. The result of enzymatic method is producing H_2O_2 which creates purple solution by oxidative coupling of 4-aminoantipyrine with 2, 4, 6-tribrpmo-3-hydroxybenzoic acid in the presence of peroxidase [48]. This color development time was reported as 30 min at 20 °C by Fossati et al. [17]. Enzymatic method is less sensitive to interferences in comparison with Jaffe method [49]. Materials which interfere in enzymatic method are bilirubin, ceftiofur and lipid at the highest concentration [49] and for Jaffe method are bilirubin, cefazolin, cefoxitin, at the highest concentration of ceftiofur, lipid [49], glucose [49,50], acetone, hemolysis, lipemia and calcium chloride which is one of the components of dialysis solutions [50]. Bonsnes and Taussky [45] indicated that concentration of picric acid has no effect on the color which is created by Jaffe reaction but this color is dependent on the concentration of alkali used. Wave lengths used for Jaffe method are 520 nm [16], 490 nm [47], and for enzymatic method are 546 nm [48] and 510 nm [48,17]. Linear ranges reported for enzymatic method are 13–1780 μmol L^{-1} at 546, 9–890 μmol L^{-1} at 510 nm [48], 0–2210 μmol L^{-1} [17] and for Jaffe method up to 300 mg L^{-1} by Beckman Creatinine Analyzer 2 [46]. Detection limits were reported for two wave lengths: 13 μmol L^{-1} for 546 nm and 9 μmol L^{-1} for 510 nm [48].

Table 2
Results of some creatinine spectrophotometric biosensors.

Refs.	Linear/Calibration range	Detection limit
[39]	Up to 2 mg dL^{-1}	
[10]	0–250 mg L^{-1}	0.76 mg L^{-1}
[11]	0–40 mg L^{-1}	3.3 mg L^{-1}

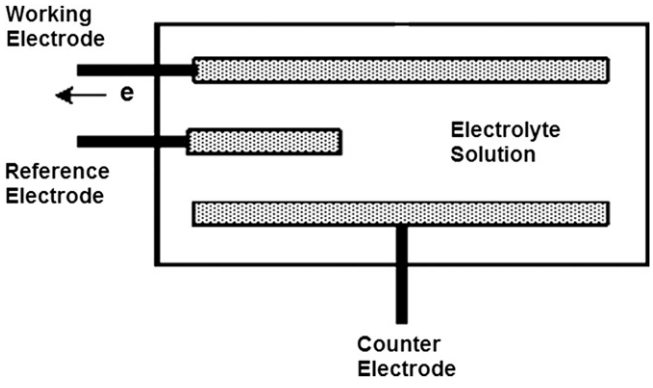

Fig. 3. A sample electrochemical biosensor.

3.2. Electrochemical transducers

Electrochemical sensors are mostly used in biomaterial sense. These sensors are based on chemical reaction. In this way, firstly, the analyte changes into another substance, then the new substance is measured by sensors. Fig. 3 indicates an electrochemical biosensor. As shown in Fig. 3 three electrodes are used in this type of biosensors and electrolyte solution contains material which should be measured. Micro electrochemical creatinine sensors use micro electrodes, which are mostly forms by metal chemical etching or lift-off techniques [51]. In most of these sensors enzymes are used as bio-receptors.

3.2.1. Potentiometric sensors

Attempts at developing potentiometric biosensors for creatinine detection began in 1976, with an ammonia-sensing electrode invented by Meyerhoff and Rechnitz. Most of the potentiometric creatinine biosensors are enzyme based. In this kind of sensors creatinine iminohydrolase (CIH) or creatinine deiminase (CD) are used as enzyme and an NH_4^+ sensing ion selective electrode is used as a transducer [5,52]. Fig. 4(b) indicates the chemical reaction which happens in this type of sensor. The advantage of this method is simplicity, as just a single enzyme is required [5].

Electrodes mostly used in potentiometric sensors are iridium oxide [53–55], Teflon cylinder [56], Pt [57], glassy carbon [27], carbon [58], graphite rod [59], hanging mercury drop [60] and the reference electrode is Ag/AgCl [54–57]. Response times are reported as 30–60 s [4], 30 s [58], 120 s [59], 60 s [27], 1–5 min [55], 4–10 s [61] and 1–2 min [62]. Some CIH immobilization methods use polyion complexes [57], chitosan membranes [4], poly vinyl alcohol –styrylpyridinium [52,55,58], p-toluenesulfonate doped polyaniline[56] and sensitive carboxylated polyvinyl chloride layer [62]. Table 3 shows some results of potentiometric sensors. Before using these sensors, the electrode should be washed with distilled water then immersed in a phosphate buffer solution [57].

3.2.2. Amperometric sensors

Basic components of amperometric biosensors are just like potentiometric biosensors with a little difference of voltage applied to electrodes. The current which is created in electrodes shows the target concentration in the sample. Most of Amperometric biosensors for measurement of creatinine use the three-enzyme method that is introduced by Tsuchida and Yoda [5] as it is shown in Fig. 4(a). In this method there are three steps: creatinine is converted to creatine, then creatine is converted to sarcosine and finally sarcosine is converted to glycine [5,63–69]. In the last step, oxygen is consumed and hydrogen peroxide (H_2O_2) is liberated. Complexity of this method inhibits further

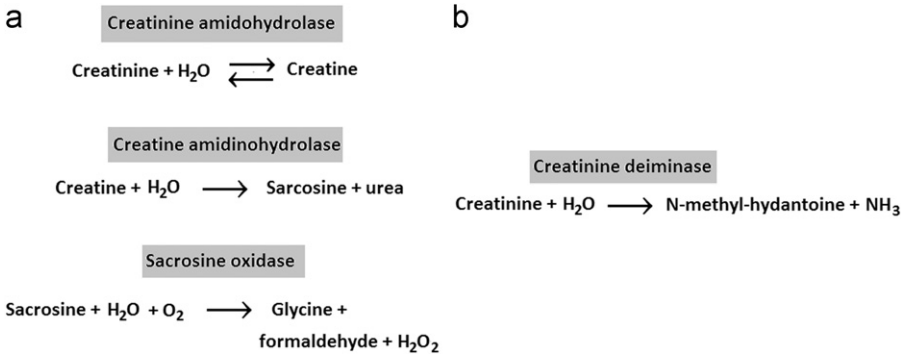

Fig. 4. Two reaction sequences which are used in creatinine electrochemical biosensors (a) creatinine to H_2O_2 by three enzymes, (b) creatinine to NH_3 by CD enzyme.

Table 3
Results of some creatinine potentiometric biosensors.

Refs.	Linear/Calibration range	Detection limit	Operational stability	Storage stability
[27]	0.5–500 μmol L^{-1}	0.5 μmol L^{-1}	90 day	
[57]	1 μmol L^{-1}–1 mmol L^{-1}			
[4]	100 μmol L^{-1}–10 mmol L^{-1}		44 day	
[103]			>1 month	>6 months
[42]	0.02–20 mmol L^{-1}	15 μmol L^{-1}	10 weeks	Longer than half a year
[55]	19–1000 μmol L^{-1}	20 μmol L^{-1}		
[104] Type1	5 μmol L^{-1}–10 mmol L^{-1}	0.39 μg mL^{-1}		10 weeks
[104] Type2	75 μmol L^{-1}–10 mmol L^{-1}	3.49 μg mL^{-1}		
[104] Type3	31 μmol L^{-1}–10 mmol L^{-1}	2.20 μg mL^{-1}		
[54]	10 μmol L^{-1}–10 mmol L^{-1}	20 μmol L^{-1}		
[56]	100–2500 μmol L^{-1}	100 μmol L^{-1}		1 month
[61] Type1	50 μmol L^{-1}–10 mmol L^{-1}	8 μmol L^{-1} (the lowest)		6 months
[61] Type2	60 μmol L^{-1}–10 mmol L^{-1}	14 μmol L^{-1}		6 months
[61] Type3	70 μmol L^{-1}–10 mmol L^{-1}	20 μmol L^{-1}		6 months
[60]	0.11–23 μg mL^{-1}	0.11 ng mL^{-1}		
[58]	40–140 μmol L^{-1} (pH sensitive electrode) 15–140 μmol L^{-1} (ammonium ion-selective electrodes)		30 day	40 day
[59]	1.23–100 μg mL^{-1}	0.37 μg mL^{-1}		
[37]	0.0025–84.0 μg mL^{-1}	1.49 ng mL^{-1}		

development because the sensitivity decreases as a result of three enzymes usage [5].

The electrochemical immunosensors use antibody–antigen based system, which is usually constructed by immobilizing particular antibody or antigen on the surfaces of the electrode. After reactions of immunoreagents with the target analytes and the labeled conjugate species, the analytes are measured through signal amplification by the labels [70]. Another Amperometric immunosensor uses antibody as receptor [41]. The anti-creatinine antibody binds to creatinine then anti-antibody glucose oxidase (which is labeled by the glucose oxidase) binds to anti-creatinine antibody to produces H_2O_2. Then it could be measured amperometricaly [71,41]. The applied voltage for this sensor is about 200 mV to overcome interference [41].

The electrodes used in amperometric sensors mostly are Platinum [5,12,18,25,26,63,65,66,71–74], carbon rod or paste [28,69], glassy carbon [41], carbon/Pt [75] and graphite/manganese dioxide [21] and reference electrode is Ag/AgCl [74,75,76]. It should be noted that not all of amperometric sensors use the three enzyme system. Mono-enzyme (CD) is used for an amperometric biosensor. The best response in this sensor is reported in the pH 8 [28]. Table 4 shows review of amperometric sensors in previous works.

The enzyme sequence hydrogen peroxide which is generated via enzymes, gives direct access to the original creatinine concentration [63]. Interfering materials for this method are creatine [63], ascorbic acid, acetaminophen and uric acid [65]. To omit electro-active substances interfering, an additional oxidizing layer on the protecting membrane of PbO_2 can be used [74,25]. For detecting hydrogen peroxide these materials were used: nafion/poly (1, 2-diaminobenzene) [64], poly (1, 3-diaminobenzene) [77] and semi permeable cellulose membrane [41].

In some three-enzyme immobilization methods poly (carbamoyl sulfonate) [65], bovine serum albumin (BSA)/glutaraldehyde matrix [67], bovine serum albumin (BSA)–Glutaraldehyde (GA) procedure [18], glutaraldehyde [63], propionic acid [78] and hydrophilic polyurethanes [79] are used. Response time for this type of creatinine sensors are reported: 360–540 s [67], 80 s [65], 98 s [25], 1 min [18], 14 s (the best) [63], 30 s [69] and 1 min [54,77].

3.2.3. pH and temperature effects

For sensor which is constructed by Suzuki et al. [67], the maximum pH dependence is shown around pH 9 and the maximum response was obtained at 37 °C. In this sensor an amperometric transducer and three-enzyme mechanism is used. pH and temperature affect the results; e.g. it is observed that at temperatures up to 40 °C activity of CD (Creatinase) increases. Hence the effects of pH and temperature on the results should be studied in electrochemical sensors.

Table 4
Results of some creatinine amperometric biosensors.

Refs.	Linear/ Calibration range	Detection limit	Operational stability	Storage stability
[75]	0.2–2 mmol L^{-1}			
[71]	0.09–90 μmol L^{-1}	40 nmol L^{-1}		
[63]	3.2–320 μmol L^{-1}	–	3 weeks	
[64]	20– 1000 μmol L^{-1}			6 months
[76]	20– 1000 μmol L^{-1}			
[65]	10– 1000 μmol L^{-1}			10 weeks
[66]	0.06–1.7 mg dL^{-1}			
[67]	0.02– 0.5 mmol L^{-1}			
[25]	1–1000 μmol L^{-1}	0.8 μmol L^{-1}		
[74]	10– 1000 μmol L^{-1}			
[73]	1–100 μmol L^{-1}			3 months
[18]	0–500 μmol L^{-1}	4.5 μmol L^{-1}	1 week	
[69]	4–100 nmol L^{-1}	2 nmol L^{-1}	1 week	
[12]	10–600 μmol L^{-1}	1 μmol L^{-1}		
[13]	(enzymeless)	0.37–	3.6 mmol L^{-1}	8.6 μmol L^{-1}
[8]	93–863 μmol L^{-1}			

3.3. ISFET based transducers

An ISFET is an ion-sensitive Field-Effect Transistor (FET) used for measuring ion concentrations in solution. As shown in Fig. 5 [80], in an ISFET the gate is sensitive to ions and pH of the solution. H^+ concentration is just like a positive potential applied to the gate of a FET. The advantage of these sensors is their simple integration in contrast with electrochemical sensors. The first ISFET was constructed by Bergveld consisted of a metal–oxide–silicon transistor [80]. Some sensors can be used for whole blood [81]. Some problems of these sensors are physical instability and light sensitivity of semiconductor structures [80].

Two main types of ISFETs are used in creatinine detection: (a) enzyme based ISFETs (EnFET) and (b) MIP based ISFETs [32].

EnFETs are designed by immobilizing enzymes on ISFETs. To increase the sensitivity of these biosensors and broaden dynamic ranges, a differential sensor can be designed and buffer solutions with different concentration and additional membranes can be used. These techniques can decrease the effect of the buffer capacity on the response too. Response of Enzyme based ISFETs depends on the buffer capacity and ionic strength of the analyte. To solve this problem, a coulometric pH control system can be implemented [80]. Type of enzyme, temperature, pH and immobilization method interferers can affect the function [82].

For manufacturing second type of ISFET based biosensors, MIP method is used because only creatinine can penetrate through it and change the voltage. Table 5 shows some results of ISFET based sensors, which are reported in some references. one enzyme immobilization way used in these types of sensors is crosslinking with Bovine Serum Albumin (BSA) in a Glutaraldehyde (GA) vapor [83] and the other one is immobilization of poly vinyl alcohol containing styrylpyridinium (PVA/SbQ) membrane [84,1] and BSA [1].

3.4. Impedometric/capacitive sensors

MIP is used as a dielectric for a capacitor that absorbs just creatinine molecules [15]. When creatinine diffuses into MIP, the dielectric constant and storage capacity is changed consequently. The difference in capacitance is relative to the amount of diffused creatinine. The capacitance of a parallel-plate capacitor constructed of two parallel plates is measured by Eq. (1).

$$C = \varepsilon_r \varepsilon_0 \frac{A}{d} \quad (1)$$

In which, ε_r and ε_0 are dielectric and electric constants respectively, A is the area of overlap of the two plates and d is the separation between them. In this type of sensors, just like potentiometric ones, CD enzyme changes creatinine into ammonium and it affect the pH of the solution (dielectric) and so the capacitance is changed. The amount of creatinine can be measured by calculating the impedance [85].

In the enzymatic method, like electrochemical way, changes in pH and temperature could affect the result and must be considered in sensor design [86]. However, some sensors are highly selective and no change in capacitance for urea, glucose and creatine has been reported [15]. 2-Acrylamido-2-Methyl-1-Propane Sulfonic acid (AMPS) as a monomer and N, N′-Methylenediacrylamide (MBA) as a crosslink agent are used to construct an MIP as a dielectric for this capacitive biosensor [15]. Response time for this type of sensor is two minutes and is better than of other sensors reported in [85]. Its storage stability is six months. Electrode used in this method is gold [15,85]. Table 6 shows some properties of impedometric sensors.

Table 5
Results of some creatinine ISFET based biosensors.

Refs.	Linear/Calibration range	Detection limit	Storage stability
[1]	20–2000 μmol L^{-1}	20 μmol L^{-1}	More than 6 months
[32]	0.199–0.787 mg mL^{-1}		
[81]	10–1000 μmol L^{-1}		
[82]	0–2000 μmol L^{-1}		
[83]	0–5 mmol L^{-1}	10 μmol L^{-1}	More than 6 months
[84]	20–1000 μmol L^{-1}	20 μmol L^{-1}	6 months
[105]	0–20 mmol L^{-1}		
[106]	44–106 μmol L^{-1}		

3.5. Chromatography

Chromatography is a set of laboratory techniques for separating a target material from a mixture. Fig. 6 shows the schematic of ion chromatography in which each species is separated. To measure an analyte by this method, the target analyte should be extracted by various techniques of chromatography then it could be measured by spectrophotometry methods. MIP can be used in purification and separation such as capillary electrochromatography [14]. Molecularly Imprinted Solid-Phase (MISP) extraction is a chromatography technique in which MIP is used as a separator [87,88]. The accuracy of detection depends on accuracy of exertion. Instruments for extraction techniques are expensive,

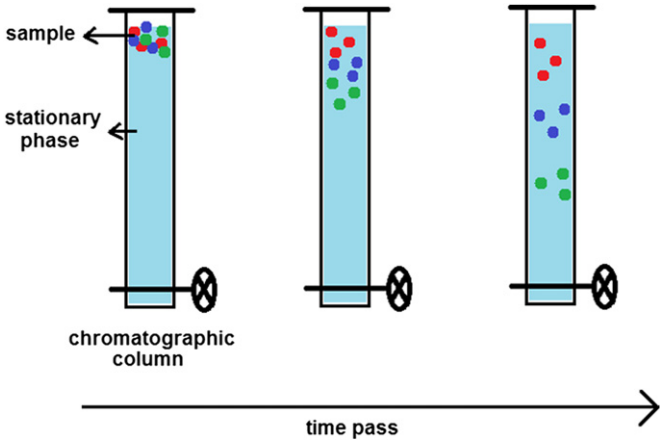

Fig. 6. Schematic of chromatography.

Table 6
Results of some creatinine impedometric biosensors.

Refs.	Linear/Calibration range	Detection limit
[15]	100–600 μmol L^{-1}	10 μmol L^{-1}
[107]	50–450 μmol L^{-1}	100 nmol L^{-1}
[34]	0.05–2 μg mL^{-1}	40 ng mL^{-1}

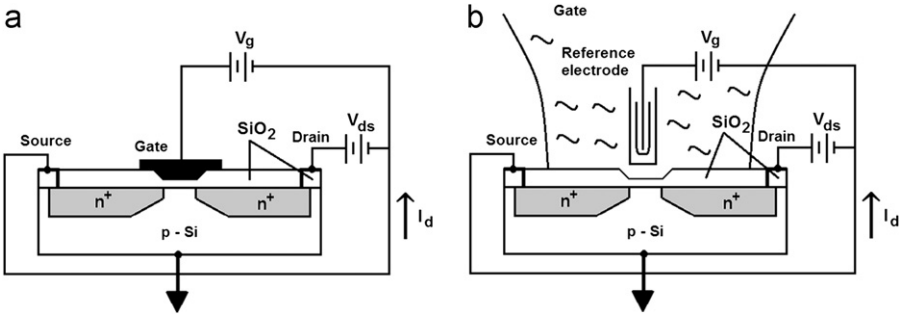

Fig. 5. FET (a) and ISFET (b) [72].

Table 7
Comparison of equations to predict glomerular filtration rate (mL/min per 1.73 m^2) from serum creatinine concentration* [97].

Equation type	Formula
Eq. (a): Serum creatinine	$GFR = 0.69^{*}[100/P_{cr}]$
Eq. (b): Cockcroft–Gault formula	$GFR = 0.84^{*}$[Cockcroft–Gault formula]
Eq. (c): Creatinine clearance	$GFR = 0.81^{*}[C_{cr}]$
Eq. (d): Average of creatinine and urea clearance	$GFR = 1.11^{*}[(C_{cr}+C_{urea})/2]$
Eq. (e): Creatinine clearance, urea clearance, and demographic variables	$GFR = 1.04^{*}[C_{cr}]^{0.751*}[C_{urea}]^{0.226*}$[1.109 if patient is black]
Eq. (f): Demographic, serum, and urine variables	$GFR = 198^{*}[P_{cr}]^{-0.858*}[\text{Age}]^{-0.167*}$[0.822 if patient is female]*[1.178 if patient is black]*$[\text{SUN}]^{-0.293*}[\text{UUN}]^{0.249}$
Eq. (g): Demographic and serum variables only (multiple regression model)	$GFR = 170^{*}[P_{cr}]^{-0.999*}[\text{Age}]^{-0.176*}$[0.762 if patient is female]*[1.180 if patient is black]*$[\text{SUN}]^{-0.170*}[\text{Alb}]^{0.318}$

Age, sex, and weight each had a P value > 0.75; none of them entered Eq. (e). Alb = serum albumin concentration (g/dL); C_{cr} = creatinine clearance (mL/min per 1.73 m^2); C_{urea} = urea clearance (mL/min per 1.73 m^2); P_{cr} = serum creatinine concentration (mg/dL); SUN = serum urea nitrogen concentration (mg/dL); UUN = urine urea nitrogen concentration (g/d).

* Cockcroft–Gault formula and creatinine clearance are adjusted for body surface area.

and therefore, it is unsuitable for routine analyses [42]. High-performance liquid chromatography (HPLC) is another technique of chromatography. In comparison with routine Jaffe method, HPLC is more precise and has less interference [16]. Overestimation of Jaffe method is clear in comparison with HPLC too [16,89]. HPLC procedures presented by Spierto et al. [16] show 100% analytical recovery in spite of 80% analytical recovery of Jaffe method. Detection limit and linear range of detection by using this method are reported 11.5 μmol L^{-1} and 0–4.4 mmol L^{-1}, respectively [18]. Other reported linear range of response is 34.6–553.3 μmol L^{-1} [92] and detection limits are 0.28 nmol L^{-1}, −3.5 μmol L^{-1} [90] and 0.05 mg dL^{-1} [91].

4. Glomerular filtration rate

Glomerular Filtration Rate (GFR) is the volume of fluid passed through kidney glomerular capillaries' wall to Bowman's capsule per unit time. It is the other way for renal functionality, but GFR measurement rarely done in laboratories [93]. Although creatinine clearance overestimates GFR, but it can be substituted for GFR [93,94]. Creatinine clearance will be discussed in next subsection. Modification of Diet in Renal Disease (MDRD) is one of popular equations for estimation of GFR (*e*GFR) which uses Serum Creatinine (*Scr*) [93,95]. It can be written as [93]:

$$eGFR = 175\ Scr^{-1.154}Age^{-0.203}(-0.742 \text{ for females and } -1.212 \text{ for African-American}) \quad (2)$$

eGFR accuracy depends inversely on serum creatinine assay [96,49]. Recently, cystatin *C*, a low molecular weight protein in blood, has been considered as an alternative for serum creatinine. But comparisons indicate that both cystatin *C* and creatinine measurement requires calibration [95].

Table 7 shows seven equations for GFR estimation. Seventh equation in this Table is multiple regression model presented by Levey et al. [97]. They compared the result of this estimation with six others ones and showed that multiple regression model provides a more accuracy in GFR estimation.

4.1. Creatinine clearance

Creatinine Clearance (C_{Cr}) as an alternative for GFR measurement is calculated by Eq. (3).

$$C_{cr} = \frac{U_{cr} \times V}{P_{cr} * 1440} \quad (3)$$

In which, U_{cr} is "creatinine concentration in 24 h collected urine", V is "urine flow rate" and P_{cr} is "creatinine concentration in plasma". The difficulty and duration of the test can be source of errors in C_{Cr} measurement. Due to the fact that daily (24 h) urinary creatinine excretion is extremely low in kidney failure [98], there are some attempts to predict it. Well known Cockcroft–Gault formula (Eq. (4)) is an estimation of creatinine clearance [99].

$$C_{cr} = \frac{(140-\text{age})(\text{wt kg})}{72 \times Scr\ (\text{mg}/100\ \text{mL})} \quad (4)$$

Some other calculations were presented in papers. They claimed that urinary creatinine depends on the muscle mass [98], hence it could be calculated by measuring Fat-Free Mass (FFM) or Body Cell Mass (BCM) and normalizing it by patient's height [100]. Firstly, 24 h U_{cr}/FFM for some patients is measured as a database for other C_{Cr} prediction of the patients, and C_{Cr} is calculated by Eq. (5) [101].

$$C_{cr} = \frac{\text{estimated } U_{cr}}{Pc_r} \quad (5)$$

Estimated U_{cr} is calculated as the mean ratio of 24 h U_{cr}/FFM. FFM or BCM is measured by a four-electrode placed two on right hand and two on right foot [101,102]. After applying current and frequency, resistance and reactance are determined by manufacturer's equation. The current and frequency of measurement is reported 800 mA, 50 KHz [102] and 0.8 mA, 50 KHz [101] respectively.

5. Conclusion

All kinds of creatinine biosensors with application for blood, serum, plasma and urine samples are investigated and compared. The lowest detection limit is reported 0.28 nmol L^{-1} for a chromatographic sensor [90]. Stability of sensors in which enzymes are use, is studied because enzyme loses its sensitivity in sequential experiments. Storage stability of most of the electrochemical sensors is more than six months, and the best operational storage is 90 day [27]. Linear range and response time have application the dialysis process. Hence some sensors, which extract serum, are improper for real time detection. The lowest response time belongs to a potentiometric sensor which is 4–10 s [61]. Another effective parameter on sensitivity is the way of enzyme immobilization in electrochemical sensors and ISFETs. The main problems in designing this kind of sensors are controlling factors, which effect on chemical reaction. Enzyme immobilization, temperature and pH affect results. Among all these sensors, MIP based sensors have the best performance. The reason is that only target molecules can penetrate through it and nothing

can affect the result; like interfering molecules, pH and temperature. So the selectivity of these sensors is higher than others.

References

[1] B. Gao, B.Y. Li, Z. Zhang, J. Chromat. B 878 (2010) 2077–2086.
[2] L. Mora, A. Cazares, M. Sentandreu, F. Toldra, Meat Sci. 84 (2010) 384–389.
[3] J. Magalhaes, A. Machado, Analyst 127 (2002) 1069–1075.
[4] N. Renault, A. Soldatkin, C. Martelet, P. Boyer, W. Sant, M. Pourciel, P. Montoriol, A. Costes, in: Proceedings of IEEE International Conference on 12th lnternational Conference on Solid State Sensors. Actuat. Microsyst. 2 (2003) 1188–1191.
[5] A. Killard, M. Smyth, Tibtech 18 (2000) 433–437.
[6] K. Sikaris, Clin. Biochem. 31 (2010) 121–128.
[7] A. Sharma, T. Jana, R. Kesavamoorthy, L. Shi, M. Virji, D. Finegold, S. Asher, J. Am. Chem. Soc. 126 (2003) 2971–2977.
[8] K. Schnabl, S. Bagherpoor, P. Diker, Ch. Cursio, J. DuBois, P. Yip, Clin. Biochem. 43 (2010) 1026–1029.
[9] B. Miller, R. Dubos, J. Biol. Chem. 121 (1937) 557–564.
[10] Sh. Ohira, A. Kirk, P. Dasgupta, Anal. Biochem. 384 (2009) 238–244.
[11] T. Songjaroen, T. Maturos, A. Sappat, A. Tuantranont, W. Laiwattanapaisal, Anal. Chim. Acta. 647 (2009) 78–83.
[12] H. Lee, Sh. Chen, Talanta 64 (2004) 750–757.
[13] J. Chen, A. Kumar, H. Chung, S. Chien, M. Kuo, J. Zen, Sens. Actuators B 115 (2006) 473–480.
[14] V. Kandimalla, H. Ju, Anal. Bioanal. Chem. 380 (2004) 587–605.
[15] T. Panasyuk-Delaney, V. Mirsky, O. Wolfbeis, Electroanalysis 14 (2002) 221–224.
[16] F. Spierto, M. MacNeil, P. Culbreth, I. Duncan, C. Burtis, Clin. Chem. 26/2 (1980) 286–290.
[17] P. Fossati, L. Prencipe, G. Bertl, Clin. Chem. 29/8 (1983) 1494–1496.
[18] D. Walsh, E. Dempsey, Anal. Chim. Acta. 459 (2002) 187–198.
[19] S. Li, J. Singh, H. Li, I.A. Banerjee, Biosensor Nanomaterials, first ed., John Wiley & Sons, 2011.
[20] D. Tsikasa, A. Wolf, A. Mitschke, F. Gutzki, W. Will, M. Bader, J. Chromatogr., B. 878 (2010) 2582–2592.
[21] Ch. Ritter, F. Heike, K. Herbert, K. Josef, L. Susanne, N. Christian, O. Helmut, P. Gabriele, S. Bernhard, S. Marieluise, S. Wolfgang, S. Gregor, Sens. Actuators, B 76 (2001) 220–225.
[22] F. Arzideh, W. Wosniok, R. Haeckel, Clin. Chim. Acta. 411 (2010) 215–221.
[23] D. Janasek, W. Vastarella, U. Spohn, N. Teuscher, A. Heilmann, Anal. Bioanal. Chem. 374 (2002) 1267–1273.
[24] F. Palmisano, P. Zambonin, D. Centonze, Fresenius J. Anal. Chem. 366 (2000) 586–601.
[25] J. Shin, Y. Choi, H. Lee, S. Choi, J. Ha, I. Yoon, H. Nam, G. Cha, Anal. Chem. 73 (2001) 5965–5971.
[26] M. Trojanowicz, A. Lewenstam, T. Krawczyk, I. Lahdesmaki, W. Szczepek, Electroanalysis 8 (1996) 233–243.
[27] Y. Shih, H. Huang, Anal. Chim. Acta. 392 (1999) 143–150.
[28] H. Kinoshita, M. Torimura, K. Kana, T. Ikeda, Electroanalysis 9 (1997) 1234–1238.
[29] S. Subrahmanyam, S. Piletsky, E. Piletska, B. Chen, R. Day, A. Turner, Adv. Mater. 12 (2000) 722–724.
[30] S. Subrahmanyam, S. Piletsky, E. Piletska, B. Chen, K. Karim, A. Turner, Biosens. Bioelectron. 16 (2001) 631–637.
[31] T. Delaney, D. Zimin, M. Rahm, D. Weiss, O. Wolfbeis, V. Mirsky, Anal. Chem. 79 (2007) 3220–3225.
[32] Ch. Lin, H. Tsai, Y. Juang, Y. Su, W. Li, R. Wang, H. Lin, J. Guo, T. Tsai, B. Liu, Proc. of IEEE Int. Conf. on circuits and systems: Testing and Diagnose 1 (2009) 1–4.
[33] M. Lee, T. Tsai, J. Thomas, H. Lin, Desalination 234 (2008) 126–133.
[34] B. Khadro, C. Sanglar, A. Bonhomme, A. Errachid, N. Renault, Procedia Eng. 5 (2010) 371–374.
[35] Ch. Huang, Analog Integr. Circ. Sig. Process 67/3 (2010) 375–381.
[36] H. Tsai, M. Syu, Anal. Chim. Acta. 539 (2005) 107–116.
[37] D. Lakshmi, B. Prasad, P. Sharma, Talanta 70 (2006) 272–280.
[38] R. Hsieh, H. Tsai, M. Syu, Biomaterials 27 (2006) 2083–2089.
[39] I. Raimundo Jr., C. Pasquini, Analyst 122 (1997) 1039–1044.
[40] Sh. Narayanan, H. Appleton, Clin. Chem. 26/8 ((1980) 1119–1126.
[41] A. Benkert, F. Scheller, W. Schoessler, B. Micheel, A. Warsinke, Electroanalysis 12 (2000) 1318–1321.
[42] A. Radomska, E. Bodenszac, S. Glab, R. Koncki, Talanta 64 (2004) 603–608.
[43] D. Lefranc, O. Schaf, R. Denoyel, J. Lefranc, R. Guieu, P. Brunet, V. Hornebecq, Microporous Mesoporous Mater. 129 (2010) 144–148.
[44] A. Hunter, W. Campbell, J. Biol. Chem. 32 (1917) 195–231.
[45] R. Bonsnes, H. Taussky, J. Biol. Chem. 158 (1945) 581–591.
[46] O. Flores, L. Sun, N. Vaziri, D. Mivada, Am. J. Med. Technol. 46/11 (1980) 792–798.
[47] J. Clarke, Clin. Chem. 7 (1961) 371–383.
[48] W. Gudert, G. Hoffmann, J. Clin. Chem. Clin. Biochem. 24 (1986) 889–902.
[49] R. Jacobs, J. Lumsden, J. Taylor, E. Grift, Can. J. Vet. Res. 55 (1991) 150–154.
[50] L. Larpent, Ch. Verger, Perit Dial Int. 10 (1990) 89–92.
[51] H. Suzuki, Clin. Chim. Acta. 334 (2003) 41–69.
[52] W. Satoh, H. Hosono, H. Yokomaku, K. Morimoto, S. Upadhyay, H. Suzuki, Sensors 8 (2008) 1111–1127.
[53] W. Satoh, H. Yokomaku, H. Hosono, H. Suzuki, Proc. of IEEE Int. Conf. Sensors (2006) 1004–1007.
[54] H. Suzuki, Y. Matsugi, Sens. Actuators, B 98 (2004) 101–111.
[55] H. Suzuki, Y. Matsugi, Sens. Actuators, B 108 (2005) 700–707.
[56] P. Pandey, A. Mishra, Sens. Actuators, B 99 (2004) 230–235.
[57] T. Osaka, Sh. Komaba, A. Amano, Y. Fujino, H. Mori, Sens. Actuators, B 65 (2000) 58–63.
[58] N. Chou, J. Chou, T. Sun, S.H. Hsiung, IEEE Sens. J. 9 (2009) 665–672.
[59] A. Patel, P. Sharma, B. Prasad, Electronalysis 20 (2008) 2102–2112.
[60] D. Lakshmi, P. Sharma, B. Prasad, Biosens. Bioelectron. 22 (2007) 3302–3308.
[61] M. Elmosallamy, Anal. Chim. Acta. 564 (2006) 253–257.
[62] M. Gutierrez, S. Alegret, M. Valle, Biosens. Bioelectron. 23 (2008) 795–802.
[63] G. Hsiue, P. Lu, J. Chen, J. Appl. Polym. Sci. 92 (2004) 3126–3134.
[64] B. Schaffar, Anal. Bioanal. Chem. 372 (2002) 254–260.
[65] A. Erlenkötter, M. Fobker, G. Chemnitius, Anal. Bioanal. Chem. 372 (2002) 284–292.
[66] J. Tombach, F. Schneider, R. Matzkies, G.Chemnitius Schaefer, Clin. Chim. Acta. 312 (2001) 129–134.
[67] H. Suzuki, H. Arakawa, I. Karube, Biosens. Bioelectron. 16 (2001) 725–733.
[68] N. Radhakrishnan, J. Park, K. Chang-Soo, The Proc. of SPIE (2007) http://dx.doi.org/10.1117/12.737092.
[69] R. Stefan, R. Bokretsion, J.V. Staden, H. Enein, Talanta 60 (2003) 1223–1228.
[70] J. Chen, F. Yan, Z. Dai, H. Ju, Biosens. Bioelectron. 21 (2005) 330–336.
[71] A. Warsinke, A. Benkert, F. Scheller, J. Fresenuis, Anal. Chem. 366 (2000) 622–634.
[72] P. D'Orazio, Clin. Chim. Acta. 334 (2003) 41–69.
[73] T. Yao, K. Kotegawa, Anal. Chim. Acta. 462 (2002) 283–291.
[74] S. Choi, S. Lee, J. Shin, J. Ha, H. Nam, G. Cha, Anal. Chim. Acta. 461 (2002) 251–260.
[75] E. Kim, T. Haruyama, Y. Yanagida, E. Kobatake, M. Aizawa, Anal. Chim. Acta. 394 (1999) 225–231.
[76] M. Osborne, H. Girault, Microchim. Acta. 117 (1995) 175–185.
[77] B. Adhikari, S. Majumdar, Prog. Polym. Sci. 29 (2004) 699–766.
[78] J. Berberich, A. Chan, M. Boden, A. Russell, Acta Biomater. 1 (2005) 193–199.
[79] J. Berberich, L. Yang, I. Bahar, A. Russell, Acta Biomater. 1 (2005) 183–191.
[80] S. Dzyadevych, A. Soldatkin, Y. Korpan, V. Arkhypova, A. El'skaya, J. Chovelon, C. Martelet, N. Renault, Anal. Bioanal. Chem. 377 (2003) 496–506.
[81] W. Sant, M. Pourciel-Gouzy, J. Launay, T. Conto, R. Colin, A. Martinez, P. Temple-Boyer, Sens. Actuators, B 103 (2004) 260–264.
[82] B. Premanode, C. Toumazou, Sens. Actuators, B 120 (2007) 732–735.
[83] A. Soldatkin, J. Montoriol, W. Sant, C. Martelet, N. Renault, Talanta 58 (2002) 351–357.
[84] A. Soldatkin, J. Montoriol, W. Sant, C. Martelet, N. Renault, Mater. Sci. Eng. C 21 (2002) 75–79.
[85] W. Ho, S. Krause, C. McNeil, J. Pritchard, R. Armstrong, D. Athey, K. Rawson, Anal. Chem. 71 (1999) 1940–1946.
[86] J. Cossar, B. Coleman, C. Ramsay, T. Atkinson, Biosens. Bioelectron. 5 (1990) 273–289.
[87] P. Sharma, D. Lakshmi, B. Prasad, Chromatographila 65 (2007) 419–427.
[88] P. Sharma, D. Lakshmi, B. Prasad, Biomed. Chromatogr. 21 (2007) 976–986.
[89] P. Yuen, S. Dunn, T. Miyaji, H. Yasuda, K. Sharma, R. Star, Am. J. Physiol. Renal Physiol 286 (2004) 1116–1119.
[90] A. Hewavitharana, H. Bruce, J. Chromatogr., B. 784 (2003) 275–281.
[91] R. Harlan, W. Clarke, J. Bussolo, M. Kozak, J. Straseski, D. Meany, Clin. Chim. Acta. 411 (2010) 1728–1734.
[92] P. Hétu, M. Gingras, B. Vinet, Clin. Biochem. 43 (2010) 1158–1162.
[93] H. Pottel, L. Hoste, F. Martens, Clin. Chim. Acta. 411 (2010) 1341–1347.
[94] W. Junge, B. Wilke, A. Halabi, G. Klein, Clin. Chim. Acta. 344 (2004) 137–148.
[95] S. Herget-Rosenthal, A. Bökenkamp, W. Hofmann, Clin. Biochem. 40 (2007) 153–161.
[96] L. Pieroni, et al., Clin. Chim. Acta. 412 (2011) 2070–2075.
[97] A. Levey, J. Bosch, J. Lewis, T. Greene, Ann. Intern. Med. 130 (1999) 461–470.
[98] Y. Mori, M. Hiraoka, N. Suganuma, H. Tsukahara, H. Yoshida, M. Mayumi, Pediatr Nephrol. 21 (2006) 683–687.
[99] D. Cockcroft, M. Gault, Nephron 16 (1976) 31–41.
[100] D. Kotler, E. Sordillo, United States Patent. 1996, patent No.: 5,722,396.
[101] C. Donadio, A. Lucchesi, G. Tramonti, C. Bianchi, Ren. Fail. 20 (1998) 285–293.
[102] G. Chertow, E. Lowrie, D. Wilmore, J. Gonzalez, N. Lew, J. Ling, M. Leboff, M. Gottlieb, W. Huang, B. Zebrowski, J. College, J. Lazarus, Clin. J. Am. Soc. Nephrol. 6 (1995) 75–81.
[103] A. Radomska, R. Koncki, K. Pyrzynska, S. Glab, Anal. Chim. Acta. 523 (2004) 193–200.
[104] S. Hassan, E. Elnemma, A. Mohamed, Electroanalysis 17 (2005) 2246–2253.
[105] B. Premanode, C. Toumazoub, Sens. Actuators, B 120 (2007) 732–735.
[106] P. Pookaiyaudom, P. Seelanan, F. Lidgey, K. Hayatleh, C. Toumazou, Sens. Actuators, B 153 (2010) 453–459.
[107] P. Boyer, J. Gal, M. Gouzy, W. Sant, A. Martinez, Sens. Actuators, B 118 (2006) 47–52.