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Biosensing methods for determination of creatinine: A review

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ABSTRACT

Creatinine is a metabolic product of creatine phosphate in muscles, which provides energy to muscle tissues. Creatinine has been considered as indicator of renal function specifically after dialysis, thyroid malfunction and muscle damage. The normal level of creatinine in the serum and its excretion through urine in apparently healthy individuals is 45–140 μM and 0.8–2.0 gm/day respectively. The level of creatinine reaches > 1000 μM in serum during renal, thyroid and kidney dysfunction or muscle disorder. A number of conventional methods such as colorimetric, spectrophotometric and chromatographic are available for determination of creatinine. Besides the advantages of being highly sensitive and selective, these methods have some drawbacks like time-consuming, requirement of sample pre-treatment, high cost instrumental set-up and skilled persons to operate. The sensors/biosensors overcome these drawbacks, as these are fast, easy, cost effective and highly sensitive. This review article describes the classification, operating principles, merits and demerits of various creatinine sensors/biosensors, specifically nanomaterials based biosensors. Creatinine biosensors work optimally within 2–900 s, potential range 0.1–1.0 V, pH range 4.0–10.0, temperature range 25–35 °C and had linear range, 0.004–30000 μM for creatinine with the detection limit between 0.01.01 μM and 520 μM. These biosensors measured creatinine level in sera and urine samples and had storage stability between 4 and 390 days, while being stored dry at 4 °C. The future perspective for further improvement and commercialization of creatinine biosensors are discussed.

1. Introduction

Creatinine (2-amino-1-methyl-5H-imidazol-4-one) is one of the components of human blood and urine. It is the final product of creatine phosphate metabolism in muscles and provides energy to muscle tissues. The determination of creatinine in biological fluids is an increasingly important clinical measurement for the evaluation of renal dysfunction, thyroid malfunction and muscle damage (Lad et al., 2008; Ruedas-Rama and Hall, 2010). The renal dysfunctions are an important agent for mortality and morbidity (prevalence: 17.2%). During last 15 years, the renal failure incidence has been doubled. The filtration rate of glomerular is reduced less than 15 mL/min in the case of progressive renal failure, which results in imbalanced serum electrolytes and accumulated metabolic byproducts including creatinine and urea. Normal level of creatinine in the serum and its excretion through urine in apparently healthy individuals is 45–140 μM and 0.8–2.0 gm per day or 24 h respectively (Kumar et al., 2017). Men usually have slightly higher creatinine level compared to women, since women have less bulk. The majority of creatine in the human body is in two forms, either the phosphorylated form making up 60% of the stores or in the free form, which makes up 40% of the stores. The creatinine level above 140 μM in human serum acts as a biomarker for renal kidney dysfunction and less than 40 μM indicates decreased muscle mass, which is a biomarker for muscular disorder. A rapid highly sensitive, selective and specific analytical device is required to safeguard the patients suffering from kidney disease, muscle damage to determine the creatinine concentration in blood and urine daily (Schenk et al., 2007; Udy et al., 2009). Hence, studying the level of creatinine in biological fluids is very helpful for diagnosis, therapy of kidney and muscle disorders. The most commonly used methods/techniques for creatinine determination are colourimetry, spectrophotometry (Campo et al., 1995), high pressure liquid chromatography (HPLC) (Yue-Dong, 1998), mass spectroscopy (Schwedhelm et al., 2000), IR spectroscopy (Pezzaniti et al., 2001), capillary zone electrophoresis (Clark et al., 2001), flow injection analysis systems with electrochemical and spectrometric detection, nuclear magnetic resonance (NMR) (Choi et al., 2002). However, these techniques had problems such as low reproducibility, lack of stability, sensitivity, interference by numerous metabolites and drugs found in biological fluids, such as glucose, fructose, ketone bodies, ascorbic acid and cephalosporins. Assay based first label-free luminescence detection technique for transcription factor activity depends on the principle binding of the transcription factor prevents the ExoIII catalyzed

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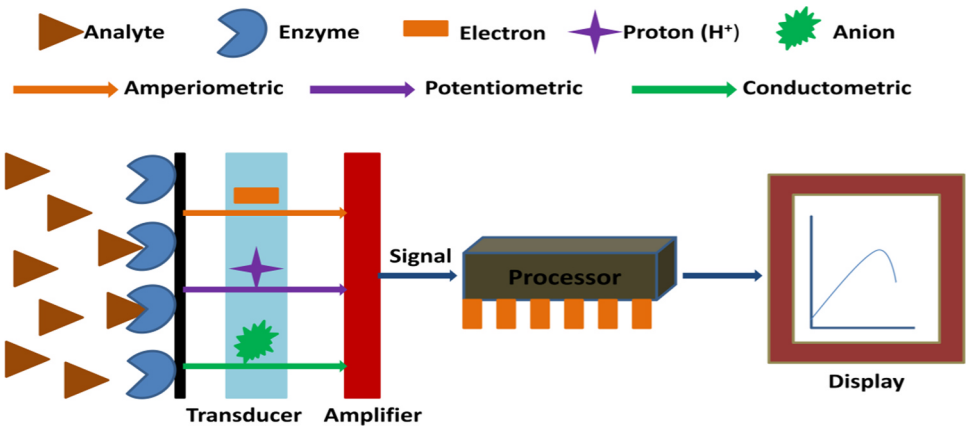

Fig. 1. Principle of various types of electrochemical sensor.

digestion of a double-stranded substrate. Luminescence assay method provides a rapid and low cost by the deregulation of transcription factor activity (Ma et al., 2011). The biosensor technology provide many advantages over these techniques for routine serum creatinine analysis, due to its simplicity, specificity, sensitivity, fast response time with reduced cost and to enable home monitoring by the patients. Creatinine detection in the point of care testing (POCT) environment has recently emerged via biosensors for whole blood, which provides a fast and reliable test results for the patient (Skurup et al., 2008). The development of creatinine biosensors has followed different paths but mainly based on potentiometric and amperometric detection (Killard et al., 2000). The amperometric and potentiometric biosensors have their own merits and demerits. However, recent trends indicate that amperometric biosensors are emerging more popular and have been commercialized successfully for the first time (Nova Biomedical, Rodermark, Germany). During the past decade, these biosensors have relied on nanotechnological platforms to enhance the surface area of biointerface region for fast electron kinetics, specific and selective detection of an analyte.

Nanotechnology deals with the properties and applications of materials at the nanoscale and is creating as a potent device to improve the execution of biosensors. In recent years, with the advancement of nanotechnology, a considerable measure of one kind of nanomaterials have been manufactured, their exceptional properties are being found step by step and their applications have incredibly propelled the execution of biosensors (Devi et al., 2012; Pundir et al., 2013). The metal oxides nanostructures have exceptional ability to propel fast electron exchange rate between electrode and the active site of the coveted enzyme (Hou et al., 2016; Miao et al., 2016). Immediately, with the progression of nanotechnology, a vital number of novel nanomaterials have been utilized and their novel properties are being gradually found and applied to build enhanced/progressed biosensors (Maeda, 2014; Pumera, 2014; Kumar et al., 2018). This article describes the present status of electrochemical creatinine sensors with particular emphasis on bionanosensors. The most commonly-used detection methods for the creatinine sensing are likewise discussed.

2. Creatinine biosensors

Biosensors combine a biological recognition element that responds to the substance being measured with a transducer, whose function is to convert an observed change into a measurable signal. The biological element can be either a biocatalyst (enzymes, microorganisms, tissue material) or a bioligand (antibody, nucleic acids and lipid layers) (Turner, 2015; Narang and Pundir, 2017). The development of an ideal creatinine sensor for detection of creatinine to diagnose renal dysfunction, thyroid malfunction and muscle damage could be a challenge for the biosensor industry. The different procedures and techniques have been used in construction of creatinine biosensors. Among them, the electrochemical creatinine biosensors have attracted the maximum scrutiny, because of their simplicity, sensitivity, specificity, rapidity and economy for routine analysis (Palchetti et al., 2009).

3. Classification of creatinine biosensors

The creatinine biosensors can be classified as electrochemical sensors, immunosensors, conductimetric biosensors, eStefan-vannzymeless/chemical sensors, nanomatetrials-based electrochemical biosensors and enzyme nanoparticles (ENPs) based biosensors as given below:

3.1. Electrochemical creatinine sensors

Electrochemical sensors have been considered as most sensitive device in monitoring of creatinine. A number of methods were designed to amplify the electronic signals so as to detect a trace amount of the analyte. Predominately, electrochemical sensors are of three types: potentiometric, amperometric and conductometric. The principles of various types of electrochemical sensors are shown in Fig. 1.

3.1.1. Potentiometric creatinine biosensors

Potentiometric biosensors are based on the principle of measure of the potential difference between a reference electrode and working electrode vs reference electrode in an electrochemical cell, when zero or no significant current flows between them. In other words, potentiometric provides information about the use of ion selective electrodes to determine changes in the concentration in an electrochemical reaction. In these biosensors, a constant potential is generated by the reference electrode, while the working electrode conveys an erratic potential which depends on the concentration of analytes (Nakazato, 2013). The change in potential at the electrode-electrolyte interface from unbalanced activities of species i in the electrolyte phase (s) and in the electrode phase (β) is calculated by the following Nernst equation:

Where E_0 represents the potential of standard electrode, R-gas constant, T-absolute temperature, F-faraday constant, ai- species activity i, and Zi - number of moles of electron involved (Yunus et al., 2013).

The potentiometric creatinine biosensors can be classified further as follow:

3.1.1.1. Ammonia-gas sensing and ammonium ion based potentiometric creatinine biosensor. The ammonia sensing electrode developed by Meyerhoff and Rechnitz was first potentiometric biosensor for creatinine detection, based on measurement of ammonia gas generated from creatinine hydrolysis by creatinine iminohydrolase (CIH) or creatinine deiminase (CD), using ammonium ion-selective electrodes. The enzyme catalyzed hydrolysis of creatinine is given

below:

$$\text{Creatinine} \xrightarrow{\text{CIH/CD}} \text{N} - \text{methylhydanton} + NH_3$$

The three enzymes, creatinine amidohydrlase (CA), creatine amidinohydrolase (CI) and urease, based system were used for construction of potentiometric cretinine biosensors (Jurkiewicz et al., 1998a,b; Premanode and Toumazoub, 2007). The following enzyme catalyzed reactions were involved:

$$\text{Creatinine} + H_2O \xrightarrow{\text{CA}} \text{Creatine}$$

$$\text{Creatine} + H_2O \xrightarrow{\text{CI}} \text{Urea} + \text{Sarcosine}$$

$$\text{Urea} + 2H_2O \xrightarrow{\text{Urease}} 2NH_3 + CO_2$$

Potentiometric methods include a non faradaic process and measurement of the potential distinction between a working electrode vs reference electrode is corresponding to the logarithm of the analyte concentration in the specimen, and is measured with respect to a dormant reference electrode.

Most of the potentiometric sensors based on gas selective/pH sensitive electrodes are covered with an immobilized CIH or creatinine deiminase (CD) membrane that catalyzes the biochemical reaction and product can then be monitored. The electrodes of various biosensors designs were inserted macroelectrodes, thick/thin films and wires, which were used to measure ammonia, oxygen, and urea.

If potentiometric biosensor is based on a field effect transistor (FET) chip, it can be exactly designed to be a particle specific FET (ISFET). This type of biosensor is of metal – oxide semiconductor FET family, in which the successive frequent metal gate electrode is replaced by an appropriately sensitive membrane and a reference electrode. The immobilization of a thin layer of enzyme on the ion selective membrane of an ISFET, results in an enzyme sensitive FET (EnFET). EnFETs are mostly based on pH sensitively. ISFETs can be founded on an ammonium gas touchy FET. The design of the underlying electrode surface and the method of enzyme immobilization utilized are imperative in characterizing the operational, sensitivity, storage stability, and also potential to inhibit interference (Fig. 2).

These systems have the upside of corresponding simplicity, since they require just a single enzyme, and depend on well established gas sensing electrode method. The interference from creatinine is also prevented. However, huge issues are caused by impedance from endogenous NH_4^+ in blood and pee, low limit of detection (LOD) in biofluids and poor soundness of the compounds. Immobilization of the recognition system on the transducer is fundamental to support biosensor operation and its reuse for longer time and savvy. Accordingly, steadiness stays one of the fundamental issues with these frameworks. A large variety of techniques have been used to find ways for producing sensors with commercial potential. These have employed entrapment (Mayerhoff and Rechnitz, 1976; Jurkiewicz et al., 1998a,b; Premanode and Toumazoub, 2007; Campanella et al., 1990a,b; Razumus et al., 1994; Osaka et al., 2000; Sant et al., 2004; Chou et al., 2009), adsorption (Kihara et al., 1986; Magalhaes and Machado, 2002; Soldatkin and Mishra, 2004), crosslinking (Soldatkin et al., 2002a,b) and covalent bonding (Jurkiewicz et al., 1998a,b; Radomska et al., 2004a,b; Grabowaska et al., 2007; Gutierrez et al., 2008; Tiwari and Shukla, 2009; Tiwari and Dhakate, 2009; Cubuk et al., 2013). A comparison of analytical properties of various potentiometric creatinine biosensors are presented in Table 1.

3.1.1.1.1. Merits. Relative simple, because these are single enzyme based and depend on well established gas-sensing electrode technologies and reusable.

3.1.1.1.2. Demerits. Interference from endogenous NH_4^+ in blood and urine, low detection limit and poor stability of enzymes.

3.1.1.2. Ion-selective electrodes based potentiometric creatinine biosensor. Ion-selective electrode is a robust platform to develop biosensors. A variety of methods of immobilization have been used including covalent, entrapment and cross-linking to associate enzymes (CA, CI, Urease, CD) onto the surface of working electrode. These ion-selective electrodes based creatinine potentiometric sensors were developed utilizing different support for immobilization, such as, cellulose acetate/polyazetidine (Razumus et al., 1994); poly (vinyl alcohol) containing stryl (Suzuki and Matsugi, 2005); biological active membrane (Jurkiewicz et al., 1998a,b); calyx[4]pyrrole (Kaçar et al., 2013) and calyx[4]pyrrole (Guinovart et al., 2017). The ion-selective electrodes exhibited fast, accurate determination in real samples, better analytical performance and enhanced recognition cations.

3.1.1.3. Flow injection potentiometric creatinine biosensor. Enzyme immobilization on the electrode surface is a crucial criterion in sensor creation, it can't control every operational needs. Immobilization techniques have hinderd some interfering substances, expansion of specific layers over and additionally underneath the catalyst layer improves impedance dismissal. However, extra layers limit diffusion of the analytes to the enzyme layer and unfortunately decline sensitivity. Coated-wire (CW) and tubular (Tu)-type membrane creatinine sensors were developed, which comprise creatinine tungstophosphate (CTP), creatinine molybdophosphate (CMP) and creatinine picrolonate (CPC) ion match edifices as electroactive materials scattered in plasticized poly (vinyl chloride) (PVC) matrix membranes (Panasyuk-Delaney et al., 2002). Tu, CW and CTP membrane sensors are joined in move through cells for discovery of stream infusion investigation (FIA) of creatinine. The inherent qualities of the locators under the hydrodynamic method of operation in a low scattering complex were resolved and contrasted and information acquired under the static method of operation.

3.1.1.4. Dibenzo-30-crown-10 (DB30C10) based potentiometric creatinine

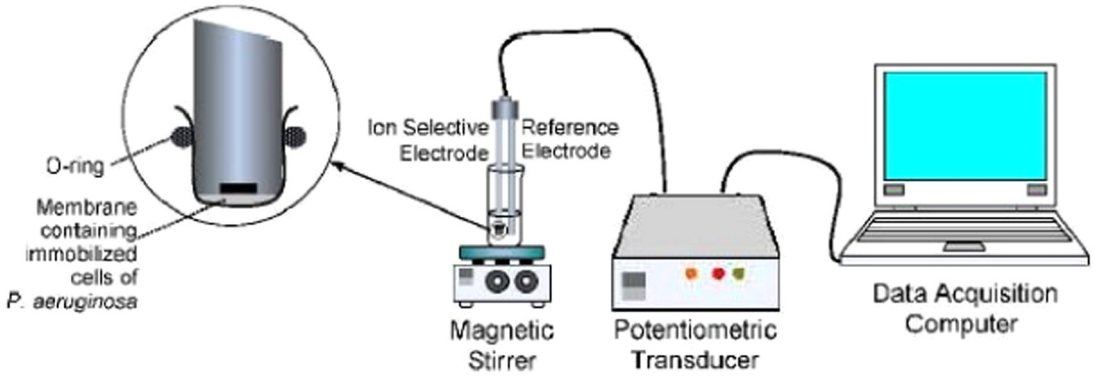

Fig. 2. Experimental setup for potentiometric biosensor.

Table 1
A comparison of analytical properties of potentiometric creatinine biosensors.

Sr no.	Support for immobilization	Enzymes	Working electrode	Method of immob-ilization	Opti-mum pH	Detection limit (μM)	Linear range (μM)	Response time (s)	Sensitivity (mv/conc)	Interfering compounds	Storage stability (days)	Samples used	Ref.
1	Cellophane dialyzing and gas permeable membrane	CIH	NH_4 gas sensing	Entrapment	8.5	520	70–8900	120–600	44.4–49.4	NH_4^+	8	Serum	Jurkiewicz et al. (1998a,b)
2	–	–	–	–	–	44	44–8800	300–360	–	–	–	Serum, Urine	Mascini and Palleschi (1982)
3	Nylon coil	CIH	NH_4^+ gas sensitive	–	–	2	–	90	–	–	–	Serum	Guilbault and Coulet (1983)
4	Collagen and pig intestine membrane	CD	NH_4 gas	–	8.7	53	88–8800	120–600	–	NH_4^+	21	Serum, Urine	Mascini et al. (1985)
5	Nylon tubes	CIH	NH_4^+ sensitive	–	8.5	10	–	–	–	–	5	Serum, Urine	Winquist and Lundstrom (1986)
6	Poly (vinyl chloride)	CD	NH_4^+ sensitive	Adsorption	8.5–9.5	44–88	88–4400	180	–	–	180	Urine	Magalhaes and Machado (2002)
7	Contolled pore glass and eupergit	GLDH, CIH	NH_4^+ sensitive	–	7.5–7.9	0.2	Upto 30	–	–	–	–	Serum, Urine	Collison and Meyerhoff (1987)
8	–	CIH	pH sensitive	–	9.5	–	50–1000	–	–	–	–	Serum, Urine	Battilotti et al. (1989)
9	Nonactine/polyphenyl acetylene	CD	En-FET/ISE	–	–	0.1/100	–	–	–	–	–	–	Osaka et al. (1998)
10	Triacetate cellulose membrane	CD	NH_3 gas sensing	Entrapment	8.0	200	200–6000	< 60	–	–	7–10	Urine, Serum	Campanella et al. (1990a,b)
11	Cellulose acetate/ polyazetidine	CD	ISE	Entrapment	–	–	100–30,000	180	35.8–37.2	Urea, ethanol amine,diethanolamine	4–9	–	Razumus et al. (1994)
12	Cubic liquid crystalline phase	CD	pH sensitive	Entrapment	–	50	500–2000	600–900	–	–	20	–	Osaka et al. (2000)
13	Controlled pore glass beads/Nylon membrane	CA, CI, Urease	NH_4^+ sensitive	Covalent	7.5	–	–	108–126	50.8–57.9	–	90	–	Premanode and Toumazoub (2007)
14	Graphite epoxy resin	CD	NH_4^+ sensitive	Covalent	7.5	10	50–1500	420	52.3	NH_4^+	30–60	Serum, Post-hemodialysate	Radomska et al. (2004a,b)
15	Polyinon complexes/ polypyrrole film	CIH	pH	–	–	1	–	–	29.8	–	–	Serum	Ho et al. (1999)
16	Poly(methyl vinyl ether)/ maleic anhydride	CD	AC impedance detection	Adsorption	–	–	–	–	–	–	–	Serum	Soldatkin et al. (2002a,b)
17	Polyinon complexes/ polypyrrole film	CIH	pH sensitive	Entrapment	6.86	1	–	–	–	–	–	–	Sant et al. (2004)
18	Poly(vinyl alcohol) containing stryl	CD	ISFET	–	7.4	20	20–1000	90–120	–	–	180	–	Suzuki and Matsugi (2005)
19	Biological active membrane	CD	ISFET	Cross-linking	7.4	10	0–5000	–	–	–	180	Serum	Jurkiewicz et al. (1998a,b)
20	Chitosan	CIH	NH_4^+ sensitive	Adsorption	7.0	100	100–1000	30–60	–	–	44	–	Soldatkin and Mishra (2004)
21	Organically modified sol gel glass and p-toluenesulfonate-doped polyaniline	CA, CI, urease	pH sensitive	Adsorption/ Entrapment	7.0	100	–	900	–	–	30	Serum	Soldatkin et al. (2002a,b)
22	Carboxylated-polyvinyl chloride	CD	NH_4^+ sensitive	Covalent	8.1	15	20–20,000	–	–	NH^+, other cations	180	Serum	Radomska et al. (2004a,b)
23	Carboxylated polyvinyl chloride	CD, urease	NH_4^+ sensitive	Covalent	–	–	–	–	–	–	180	–	Grabowaska et al. (2007)
24	PVA-SbQ	CIH	NH_3 gas sensing	–	8.5–9.5	20	–	60	–	–	–	–	Rasmussen et al. (2007)

(*continued on next page*)

Table 1 (*continued*)

Sr no.	Support for immobilization	Enzymes	Working electrode	Method of immob-ilization	Opti-mum pH	Detection limit (μM)	Linear range (μM)	Response time (s)	Sensitivity (mv/conc)	Interfering compounds	Storage stability (days)	Samples used	Ref.
25	PVA-SbQ	CD	pH sensitive	–	10	20	–	10	–	–	–	Serum	Madaras and Buck (1996)
26	Polyvinyl alcohol	CD	Chem FET	Entrapment	–	–	10–1000	300	30	–	7	–	Kihara and Yasukawa (1986)
27	Directly onto gate	CA, CI, urease	ISFET	–	6–8	–	0–20,000	–	–	–	–	Urine, Serum	Campanella et al. (1990a,b)
28	Nylon membrane	CD	–	–	7.4	0.3	–	30	58.78	–	100	–	Hsiung et al. (2010)
29	Polyvinyl chloride	CD	NH_4^+ sensitive	Covalent	–	–	–	–	–	–	–	Serum	Gutierrez et al. (2008)
30	Carboxylated-polyvinyl chloride	CD, urease	NH_4^+ sensitive	Covalent	7.5	0.1	–	60–120	50	–	–	–	Tiwari and Dhakate (2009)
31	CHIT-SiO_2 –MWCNTs	CIH	–	Covalent	7.0	–	–	–	–	–	240	–	Tiwari and Shukla (2009)
32	CHIT-g-PANI	CIH	–	Covalent	7.0	–	–	–	–	–	300	–	Kubo et al. (1983)
33	Conductive layer	CD	NH_4^+ sensitive	–	7.5	3	5–255	–	–	–	–	–	Pookaiyaaudom et al. (2011)
34	Chemical current conveyors	CD	NH_4^+ sensitive	–	7.4	–	44–106	–	–	–	–	–	Kubo and Karube (1986)
35	AuNP/Calix arene	CI, SOx	Nafion coated copper plating	Covalent	4	0.01	0.01–0.1	60	–	–	35	–	Busono et al. (2015)
36	Molecular imprinting polymers (MIP)	CI	Epoxygraphi-te matrix	Adsorption	5	7	9–100	–	–	–	28	Urine	Guinovart et al. (2017)
37	Calyx(4) pyrrole	CA	Ion-selective	Non-covalent entrapment	–	10	1–10	–	–	–	–	–	Kaçar et al. (2013)
38	pH-sensitive	–	Ammonium ion	Entrapment	–	40	40–140	30	–	–	40	–	Busono (2015)
39	Calyx[4]pyrrole	CA	Polymeric membrane	–	–	1	1–10	–	–	–	–	–	Du et al. (2015)
40	Polymeric ion	CA	Ammonium ion	Covalent	–	20	20–2000	–	–	–	180	–	Han et al. (2016)
41	pH-sensitive	CIH	Ammonium ion selective	Entrapment	–	–	40–140	30	–	–	40	–	Chou et al. (2009)
42	PVC-NH_2 membrane	CA	Ammonium selective	Covalent	7.20	–	–	–	–	–	10	–	Cubuk et al. (2013)
43	Calix[4]pyrrole	CA	Ion-selective	–	–	–	1–10,000	–	–	–	–	Urine	Guinovart et al. (2017)

Abbreviations: CI = creatinine iminiohydrolase; CD = creatinine deaminase; GLDH = glutamate dehydrogenase, ISE = ion-sensitive electrode; En-FET = Enzyme field-effect transistor; ISFET = ion-sensitive field effect transistor, CA = creatinine amidohydrolase, CI = creatine amidinohydrolase; PVC SbQ = Poly(vinyl alcohol)-styryl pyridinium; SiO_2 = silicone oxide; MWCNTs = multiwalled carbon nanotubes; CHIT = chitosan; CHIT-g-PANI = Chitosan grafted polyaniline.

Creatinine acceptor: creatininase, Signal receptor: [NH_4^+].

Working mechanism: .

a) CD = Creatinine + $H_2O \xrightarrow{\text{Creatinine deiminase}} NH_4^+ + N-$ methylhydantoin.

b) Urease = Urea + $2H_2O \xrightarrow{\text{Urease}} 2NH_3 + CO_2$.

c) CIH = Creatinine $\xrightarrow{\text{CIH/CD}} N-$ methylhydanton + NH_3.

d) GLDH = 2 − Oxoglutarate + NH_4^- + NAD(P)H $\xrightarrow{\text{GLDH}} L-$ glutamate + NAD(P) + H_2O_2.

CA, CI, SOx = Creatinine + $H_2O \xrightarrow{\text{CA}}$ Creatinine

e) Creatine + $H_2O \xrightarrow{\text{CI}}$ Urea + Sarcosine .

Sarcosine + O_2 + $H_2O \xrightarrow{\text{SOx}}$ Glycine + HCHO + H_2O_2

biosensor. Three types of enzymeless creatinine potentiometric membrane sensors were fabricated utilizing dibenzo-30-crown-10 (DB30C10) with, potassium tetrakis (p-chlorophenyl) borate, dibenzo-30-crown-10 alone and potassium tetrakis (p-chlorophenyl) borate alone. These were consolidated in a PVC matrix membrane plasticized with o-nitrophenyl octyl ether or dioctylphthalate (Elmosallamy, 2006). These creatinine biosensors depended on the neutral carrier alone or neutral carrier with anionic added substances or anionic added substances alone that have same potentiometric response characteristics.

3.1.1.5. Electronic tongue based potentiometric creatinine biosensor. An electronic tongue (ET) made out of scaled down metallic sensors (metal of high purity and alloys) and particle particular cathodes with PVC dissolvable polymeric films were produced for location of urinary creatinine level to analyze urinary dysfunctions (Lvova et al., 2009). The ET exhibited a good predictive power for the content of alkali-metal ions, urinary creatinine, total phosphorous and chloride anions.

3.1.1.6. Molecular imprinted polymers based potentiometric creatinine biosensor. Two types of molecular imprinted polymer creatine sensors based on solid contact electrodes potentiometrically assessed. The MIP polymeric material was utilized to dope PVC-membrane selective electrodes. Sensitive membrane were provided by shuffling *o,*NPOE as a plasticizer and shifting measures of the detecting polymer. The electrodes were construct utilizing (MIP/MAA) and (MIP/2-VP) as electroactive materials for conviction of creatinine concentration in sera and urine. In this mechanism ionic charge exchange occurring at the membrane during the binding of (creatine) to the membrane MIP receptor sites produces an excess of surface charge, based on blocked interface between an ionic conductor (membrane), electronic conductor and hence they show constrained soundness (Kamel and Hassan, 2016) (Fig. 3).

3.1.2. Amperometric creatinine biosensors

Amperometry is a quite sensitive electrochemical technique in which the signal of interest is current that is linearly dependent on the target concentration by applying a constant bias potential. In this method, taking advantage of the fact that certain electroactive species are oxidized or reduced (redox reactions) at inert metal electrodes driven at a constant applied potential (Ding et al., 2008). An amperometric biosensor contains two or three electrodes. The previous include comprise of a reference and a working electrode. Application of the two-electrode system to biosensors is limited, because at high current flow, potential control becomes difficult as a result of sizable IR drop. Rather, the third electrode is commonly introduced as an auxiliary counter electrode having a large surface area to make most of current flows, between the counter and working electrodes, given potential is still applied between the working and the reference electrodes (Sadeghi, 2013). The amperometric biosensors also have the advantages of being more sensitive, rapid, inexpensive and disposable as compared to conductometric and potentiometric biosensors.

These amperometric biosensors can be divided into following sub classes:

3.1.2.1. First generation dissolved oxygen meter-based amperometric creatinine biosensors. In first generation dissolved oxygen (DO) meter-based amperometric creatinine biosensor, Clark oxygen electrodes represents the simplest forms of amperometric biosensors. This biosensor measures the reduction of oxygen at a platinum working electrode in reference to an Ag/AgCl reference electrode at a given potential. DO-meter based creatinine biosensors are based with respect to immobilization of CA, CI, SOx, CD, glutamate dehydrogenase (GLDH), glutamate oxidase (GLOx) and nitrifying bacteria onto membrane as sensing part of the combined electrode of the DO meter (Kubo et al., 1983; Nguyen et al., 1991; Rui et al., 1992; Suzuki et al., 2001).

The DO meter biosensors are based on the expenditure of oxygen as identified by an oxygen electrode. A specific creatinine biosensor consisting of immobilized CD and nitrifying bacteria has been produced for the estimation of creatinine (Kubo et al., 1983). This sensor depends on the amalgamation of an enzyme reaction and the bacterial metabolism, where CD hydrolyzes creatinine to N-methylydantoin and ammonium ion and ammonia produced is successively oxidized to nitrite and nitrite by nitrifying bacteria. The bacteria have not been completely characterized but are known to be a mixed culture of *Nitrosomonas* sp. and *Nitrobacter* sp. The sequence of reactions is as follows:

$$\text{Creatinine} + H_2O \xrightarrow{\text{Creatinine deiminase}} NH_4^+ + \text{N} - \text{methylhydantoin}$$

$$NH_4^+ \xrightarrow{\text{Nitrosomomas sp.}} NO_2^- \xrightarrow{\text{Nitrobacter sp.}} NO_3^-$$

The reacting bacteria utilizes oxygen so where decrease is detected by an oxygen electrode.

Further DO-meter creatinine biosensors have been developed using CA, CI and SOx enzymes co-immobilization on the surface of membrane of a Clark-type electrode responsive to oxygen (Nguyen et al., 1991; Tsuchida and Yoda, 1983). The coupling of these three enzymes allows the transformation of creatinine without coenzymes. The reaction sequence is as follows:

$$\text{Creatinine} + H_2O \xrightarrow{CA} \text{Creatinine}$$

$$\text{Creatine} + H_2O \xrightarrow{CI} \text{Urea} + \text{Sarcosine}$$

$$\text{Sarcosine} + O_2 + H_2O \xrightarrow{SOx} \text{Glycine} + HCHO + H_2O_2$$

The reaction of creatinine in first step leads to oxygen consumption in reaction at third step.

Different methods were used for immobilization of enzymes onto membrane, mounted on the sensing part of the DO meter, such as

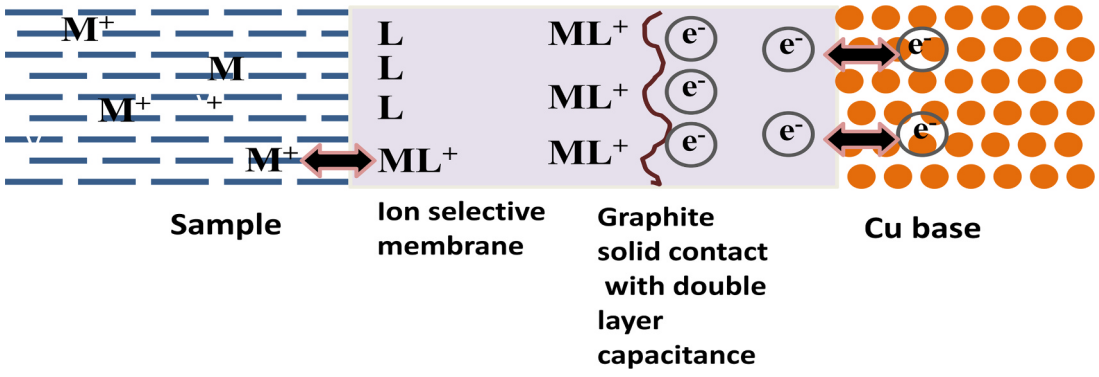

Fig. 3. Schematic representation of all relevant interfaces within graphite solid contact ion selective electrode.

Table 2
A comparison of analytical properties of DO metric creatinine biosensors.

Sr No.	Support for immobilization	Enzymes	Method of immobilization	Optimum pH	Detection limit (μM)	Linear range (μM)	Response time (s)	Interfering compounds	Storage stability (days)	Samples used	Ref.
1	Triamine and acetyl cellulose membrane	CD, nitrifying bacteria	Covalent	8.5	50	44–8840	180	No interference	300 assays over 21 days	Serum	Nguyen et al. (1991)
2	Poly(ϒ-methyl-L-glutamate)	CD, Nitrifying bacteria	Entrapment	8.5	44	88–8800	60	No interference	–	Urine	Rui et al. (1993a), (1993b)
3	Polypropylene	CA,CI, SOx	Entrapment	8.0	3	3–1000	< 60	Creatinine and Sarcosine	100 assays over 90 days	–	Rui et al. (1992)
4	Propylamine and succinate CPG	CD, GLDH, GLOD	Crosslinking	8.0	100	100–5000	180	–	–	–	Suzuki et al. (2001)
5	Propylamine and succinate CPG	CD, GLDH, GLOD	Crosslinking/ covalent	8.0	20/100	100–2000	120	Ascorbic acid, ATP, GTP	90% within 30 days	–	Rui et al. (1993a), (1993b)
6	Propylamine and succinate CPG	CD, GLDH, GLOD	Crosslinking/ covalent	8.0	200	200–5000	–	–	–	–	Kinoshita et al. (1997)
7	Silicone gas permeable membrane	CA, CI, SOx	Crosslinking	9.0	20	20–500	360–540	–	–	Serum	Tsuchida and Yoda (1983)
8	Silicalite, pH-FET	CA, DEAE	Adsorption	7.4	5	–	–	No interference	390	Urine	Ellairaja et al. (2017)
9	Rhodamine B dye Au^{3+}	CA	Covalent	–	0.005	0.054–15	–	–	–	Serum	Nanda et al. (2015)
10	DCFH-DA	CA, Urea, Glucose, Lactose	–	–	–	–	–	–	–	–	Raveendran et al. (2017)

Abbreviations: CD= creatinine deaminase, CA= creatinine amidohydrolase, CI= creatine amidinohydrolase, SOx= sarcosine oxidase, GLDH= glutamate dehydrogenase, GLOD= glutamate oxidase, CPG= controlled pore glass, ATP= adenosine triphosphate, GTP= guanosine triphosphate.

Creatinine acceptor: creatininase, Signal receptor: Dissolved O_2 electrode.

Working mechanism: .

$$\text{CD, GLDH, GLOD} = \text{Creatinine} + H_2O \xrightarrow{\text{CD}} NH_4^+ + \text{N} - \text{methylhydantoin}$$

a)
$$2 - \text{Oxoglutarate} + NH_4^- + \text{NAD(P)H} \xrightarrow{\text{GLDH}} \text{L} - \text{glutamate} + \text{NAD(P)} + H_2O_2 \cdot$$
$$\text{L} - \text{glutamate} + O_2 + H_2O \xrightarrow{\text{GLOD}} 2 - \text{Oxoglutarate} + NH_4^+ + H_2O_2$$

b) $\text{Urease} = \text{Urea} + 2H_2O \xrightarrow{\text{Urease}} 2NH_3 + CO_2.$

$$\text{CA, CI, SOx} = \text{Creatinine} + H_2O \xrightarrow{\text{CA}} \text{Creatinine}$$

c)
$$\text{Creatine} + H_2O \xrightarrow{\text{CI}} \text{Urea} + \text{Sarcosine} \quad \cdot$$
$$\text{Sarcosine} + O_2 + H_2O \xrightarrow{\text{SOx}} \text{Glycine} + \text{HCHO} + H_2O_2$$

d)
$$\text{Nitrifying bacteria} = \text{Creatinine} + H_2O \xrightarrow{\text{Creatinine deiminase}} NH_4^+ + \text{N} - \text{methylhydantoin}$$
$$NH_4^+ \xrightarrow{\text{Nitrosomomas sp.}} NO_2^- \xrightarrow{\text{Nitrobacter sp.}} NO_3^- \quad .$$

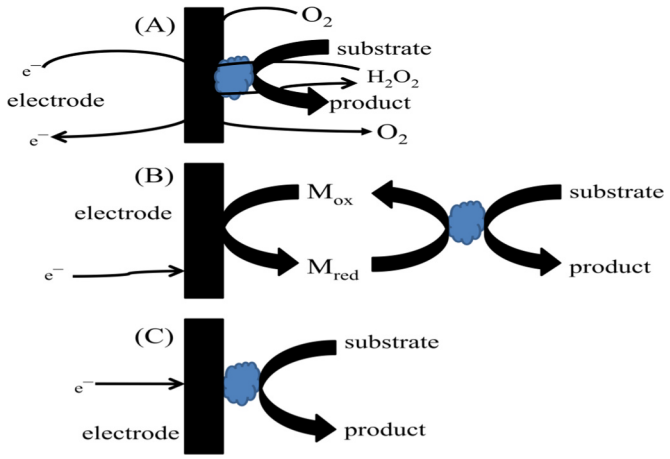

Fig. 4. Reaction scheme of biosensors based on the 1st, 2nd & 3rd generation creatinine biosensor.

entrapment, cross-linking and covalent. Table 2 compares the analytical properties of various DO meteric based creatinine biosensors.

3.1.2.1.1. Merits. Easy to use, can be used at the bedside of patient/outside the laboratory by common man.

3.1.2.1.2. Demerits. Interference by atmospheric O_2.

3.1.2.2. Second generation amperometric creatinine biosensor. The second generation amperometric creatinine biosensor, a flow injection biosensor system was likewise developed for creatinine with a single injection and one detector. The amperometric detection of creatinine was based on coupled reactions of three successively aligned enzyme reactors, CD, GLDH and GLOD. The reactions were as follow:

$$\text{Creatinine} + H_2O \xrightarrow{CD} NH_4^+ + N - \text{methylhydantoin}$$

$$2 - \text{Oxoglutarate} + NH_4^- + NAD(P)H \xrightarrow{GLDH} L - \text{glutamate} + NAD(P) + H_2O_2$$

$$L - \text{glutamate} + O_2 + H_2O \xrightarrow{GLOD} 2 - \text{Oxoglutarate} + NH_4^+ + H_2O_2$$

Ammonia produced by the enzymatic hydrolysis of creatinine was changed over to glutamate and the oxygen utilization, because of oxidation of glutamate by GLOD, was identified with an oxygen electrode.

3.1.2.3. Third generation amperometric creatinine biosensors. The third generation amperometric creatinine biosensors, fundamental components of amperometric biosensors are recently like potentiometric biosensors with a little contrast of voltage applied to electrodes. The current created in electrodes shows the target concentration in the sample. The majority of amperometric creatinine biosensors use the three-enzyme method introduced by Tsuchida and Yoda (1983). This includes the three-stage conversion of creatinine to creatine, creatine to sarcosine and sarcosine to glycine. At the last stage utilization of electrochemically discernible oxygen and liberation of hydrogen peroxide (H_2O_2) occurs. The enzyme catalyzed reactions of creatinine are appeared as:

$$\text{Creatinine} + H_2O \xrightarrow{CA} \text{Creatine}$$

$$\text{Creatine} + H_2O \xrightarrow{CI} \text{Urea} + \text{Sarcosine}$$

$$\text{Sarcosine} + O_2 + H_2O \xrightarrow{SOx} \text{Glycine} + HCHO + H_2O_2$$

The final step of the sequence involves the flavin containing enzyme sarcosine oxidase, which reacts as follows:

$$\text{Sarcosine} + SOx(FAD^+) \rightarrow \text{Glycine} + HCHO + SOx(FADH_2)$$

$$SOx(FADH_2) + O_2 \rightarrow SOx(FAD^+) + H_2O_2$$

$$H_2O_2 \rightarrow 2H^+ + O_2 + 2e^-$$

Detection of H_2O_2 liberation is selected methods in amperometric systems, although oxygen electrodes have also been used (Kubo et al., 1983; Nguyen et al., 1991; Rui et al., 1992; Tsuchida and Yoda, 1983). This decision was because of the classic problems related with interference at oxygen electrodes (i.e the high potentials required to bring about its reduction). Amperometry usually needs a system comprising of a reference, a counter (auxiliary) and working electrodes. The most common reference electrodes are the Ag/AgCl or the saturated Hg_2Cl_2 and the counter electrodes is usually an inert metal, such as platinum or stain-less steel. The key procedure in electrochemical reactions is the exchange of electrons between the working-electrode surface (area of interest) and the species at the interfacial area (in solution or those immobilized at the electrode surface). The surface topography and the nature of the functional groups on the surface significantly affect the kinetics of the reaction. The working electrode materials for creatinine biosensors incorporate platinum as a bare electrode or as a disk platinized gold, platinized shapable electroconductive (SEC) films, cellulose acetate, PbO_2 oxidizing layer, polyvinyl alcohol, poly(carbomoyl sulfonates)-hydrogel and carbon-paste electrodes (CPEs) alone or mixed with platinum powder. This platinum provides a highly catalytic surface, where H_2O_2 oxidation can continue at a quickened rate. Platinum, silver, carbon and Ag/AgCl ink can likewise be used in screen-printing methods to create thick film and thin film sensors for the fabrication of miniaturized, planer, solid state electrodes (Killard and Malcolm, 2000; Lad et al., 2008) (Fig. 4).

Different methods for immobilization were used for construction of enzyme-based amperometric creatinine biosensors, for example, entrapment (Sakslund and Hmmerich, 1992; Schneider et al., 1996; Shin et al., 2001; Tombach et al., 2001; Erlenkotter et al., 2002), cross-linking (Tsuchida and Yoda, 1983; Madaras et al., 1996; Trojanowicz et al., 1996; Khan and Wernet, 1997; Shih and Huang, 1999; Walsh and Dempsey, 2002), and adsorption (Yamato et al., 1995; Osborne and Girault, 1995; Kim et al., 1999). A comparison of analytical properties of various amperometric creatinine biosensors is shown in Table 3.

3.1.2.3.1. Merits. Superb operational stability, long storage lifetimes, moderately short response time and high sensitivity.

3.1.2.3.2. Demerits. Less sensitive, interference by creatinine and complex.

3.1.2.4. Chronoamperometric determination of creatinine based on the organic nickel (II) complexes catalytic systems. Creatinine and urea are measured with the assistance of catalytic activity of organic nickel (II) edifices in the electrochemical oxidation of creatinine and urea (Kozitsina et al., 2009). The signals of electrocatalytic oxidation of the concentrated carbonyl-containing amines in demonstrate arrangements were acquired.

3.1.2.5. Multiple enzymes system based creatinine sensors. Creatinine is changed over into electroactive H_2O_2 by three consecutive enzymatic reactions with three different enzymes. The proportion and measure of these enzymes in the enzyme solution have a big affect on the performance of the creatinine sensors. Several groups have prepared sensors with enzyme solutions with various compositions of the three enzymes. These compositions vary significantly from system to system, depending on the method of preparation and sensor structure (Hsiue et al., 2004). However, multiple enzymes promote the integration of electron transfer from the enzyme to the transducer. The biosensor exhibited optimum pH 7.25, LOD 3.2 μM, linear range 3.2–320 μM (Hsiue et al., 2004); temp 37 °C, storage stability 30 days (Berberich et al., 2005); LOD 2.6 μM, response time 70 s, linear range 4–620 μM and storage stability 720 days (Stredansky et al., 2017). The ENPs/GCE multiple enzymes based biosensor showed optimum response at 0.1 V

Table 3
A comparison of analytical properties of amperometric creatinine biosensors.

Sr no.	Support for immobilization	Enzymes	Working electrode	Method of immobilization	Optimum pH	Detection limit (μM)	Linear range (μM)	Response time (s)	Sensitivity μA/μM/cm^2	Potential applied (V)	Interfering compounds	Storage stability (days)	Samples used	Ref.
1	Cellulose acetate	CA, CI, SOx,	Pt	Crosslinking	6–10	8.8	Upto 880	20	–	0.65	–	270	–	Sakslund and Hammerich (1992)
2	Controlled pore glass	CA, CI, SOx	Pt	Entrapment	7.7	25–200	25–750	–	0.0000208	0.65	–	180	–	Schneider et al. (1996)
3	Polypyrrole doped with sulfonated phenoxy resin	CA, CI, SOx	–	Adsorption	–	200	200–5000	100	–	0.4	–	–	Serum	Osborne and Girault (1995)
4	Gas permeable membrane	CD	–	Adsorption	8.5–9.5	–	20–1000	–	0.000001	0.525	–	–	–	Kim et al. (1999)
5	Poly-2-hydroxyethyl methy-acrylate	CA, CI, SOx	Pt	Crosslinking	7.3–7.4	30	Upto 2000	300	0.0000139	0.6	Creatine	90	Serum	Trojanowicz et al. (1996)
6	Poly (1,3-diaminobenzene)	CA,CI, SOx	Plati-nized Au	Crosslinking	–	20	900–1200	60	–	0.65	Creatine, sarcosine	30	–	Kim et al. (1999)
7	Poly (carbamoyl) sulfonate hydrogel matrix	CA, CI, SOx	Pt	Entrapment	7.0–8.0	0.3	1–150	20	0.034	0.6	Low selectivity	180	Serum	Shin et al. (2001)
8	Polypyrrole	CIH	Pt	Crosslinking	–	88	Upto 2000	–	–	0.3	–	5	–	Khan and Wernet (1997)
9	Platinized-SECC-(shapeable electro-conductive) film	CA, CI, SOx	–	Crosslinking	–	1–2	10–5000	–	0.023	0.4	Creatinine, sarcosine	30	–	Shih and Huang (1999)
10	Ferrocene embedded carbon	CA, CI, SOx, Perox-idase	–	–	8.0	0.01	Upto 15	120	–	0.1	No inter-ference	–	Serum	Yao and Kotegawa (2002)
11	Carbon paste electrode	CA, CI, SOx	–	Adsorption	7.5	200	200–2000	90	–	0.5	–	–	–	Benkert et al., 2000
12	Polyaniline	CD	Glassy carbon	Crosslinking	7.5	0.5	0.5–500	60	–	0.2	NH^+, other cations	60	Serum	Walsh and Dempsey (2002)
13	PbO_2 oxidizing layer over HPU	CA, CI, SOx	Pt	Entrapment	–	0.8	1–1000	98	–	0.8	–	35	Serum	Tombach et al. (2001)
14	Poly (carbamoyl) sulfonate hydrogel with nafion	CA, CI, SOx	Pt	Entrapment	7.5	5	5–150	–	0.005	0.6	–	–	–	Erlenkotter et al. (2002)
15	Polished Pt electrode with alumina and diamond suspension	CA, CI, SOx	Pt	Crosslinking	7.4	4.5	4.5–500	60	–	0.7	–	–	–	Yamato et al. (1995)
16	Polyvinyl alcohol	CA, CI, SOx	Pt	–	7.6	10	10–1000	104	0.0001256	0.8	–	–	–	Suzuki and Matsugi (2005)
17	Nafion/poly (1,2-diaminobenzene)	CA, CI, SOx	Pt disc	–	7.5	–	1–100	–	–	0.5	No inter-ference	90	Serum	Hsiue et al. (2004)
18	Poly (carbamoyl) sulfonate hydrogel matrix	CA, CI, SOx	Pt	Entrapment	7.4	–	5–1000	25–80	0.00024–0.00046	0.6	–	75	–	Erlenkotter et al. (2002)
19	Carbon paste electrode	CA, CI, SOx	Ag wire	–	7.6	0.002	0.004–0.1	30	–	0.65	–	–	–	Guilbault et al. (1980)
20	Poly-propylene	CA, CI, SOx	Pt	–	7.0	–	3.2–320	–	–	–	–	–	Serum	Stefan-van Staden et al. (2006)
21	Carbon paste electrode	CA, CI, SOx	Ag wire		7.6	0.004–0.006	0.004–0.4	–	–	0.42–0.65	–	–	–	Guo and Guo (2005)

(*continued on next page*)

Table 3 (*continued*)

Sr no.	Support for immobilization	Enzymes	Working electrode	Method of immobilization	Opti-mum pH	Detection limit (μM)	Linear range (μM)	Response time (s)	Sensitivity μA/μM/cm^2	Potential applied (V)	Interfering compounds	Storage stability (days)	Samples used	Ref.
22	AuNP/CHIT/ c-MWCNT	CA, CI, SOx	Glassy carbon	Crosslinking	7.5	0.5	0.5–1000	4	–	0.2	No inter-ference	180	–	Maeda (2014)
23	PANi	CA, CI, SOx	Carbon	Adsorption	7.25	50	50–1000	10	–	0.4	–	30	Serum	Kamel and Hassan (2016)
24	$CaCl_2$, PEG. HECS	CA, CI, SOx, HRP	Carbon	Crosslinking	7.25	50	5–1000	40	–	–	–	30	–	Du et al. (2015)
25	Ammonium ion	CA, Urea	Copper poly-aniline	–	–	0.5	1–125	15	–	–	–	–	Serum	Marchenko et al. (2016)

Abbreviations: CD= creatinine deminase, CA= creatinine amidohydrolase, CI= creatine amidinohydrolase, SOx= sarcosine oxidase, CIH= creatinine iminiohydrolase, Pt= platinum, Au= gold, SEC= shapeable electroconductive film, HPU= hydrophilic polyurethanes, PbO_2= lead dioxide.
Creatinine acceptor: creatininase, Signal receptor: working electrodes.
Working mechanism: .

a) $CD = Creatinine + H_2O \xrightarrow{CD} NH_4^+ + N - methylhydantoin.$

b) $Urease = Urea + 2H_2O \xrightarrow{Urease} 2NH_3 + CO_2.$

$CA, CI, SOx = Creatinine + H_2O \xrightarrow{CA} Creatinine$

c) $Creatine + H_2O \xrightarrow{CI} Urea + Sarcosine$.

$Sarcosine + O_2 + H_2O \xrightarrow{SOx} Glycine + HCHO + H_2O_2$

against Ag/AgCl, within 2 s at a pH 6.0 and 25 °C, LOD 0.01 μM and good correlation coefficient (R^2 = 0.99) with a standard enzymic colorimetric method, storage stability 240 days (Kumar et al., 2017). The multiple enzymes base modified electrode showed simplicity of construction, operation stability, low cost and were highly selective.

3.2. Conductometric creatinine biosensors

Recently, a novel exceptionally delicate and stable conductometric creatinine biosensor was developed (Isildak et al., 2012). The principle of the detection depended on the way that many biochemical reactions in solution create changes in the electrical resistance between two parallel electrodes. The biosensor depends upon a solid state contact ammonium sensitive sensor. Creatininase was chemically immobilized on the surface of the solid state contact ammonium sensitive membrane by means of the glutaraldehyde covalent attachment method. LOD of the biosensor was 2×10^{-6} M and the response time was < 10 s in phosphate buffer pH 7.20. The linear dynamic range of the biosensor was 1×10^{-1}–9×10^{-6} M creatinine concentration in phosphate buffer, pH 7.20. The biosensor displayed great operational and storage stability for at least 4 weeks at 4 °C. The conductometric transducers have significant advantage since they are constructed in one way with high similarity, rough and moderately cheap with no requirement for a reference electrode.

3.3. Creatinine immunosensors

Biosensors consolidating immunology and chip based electrochemistry are called immunosensors. Like regular immunoassay, these devices are depends on the principles of solid phase immunoassay with an antibody or antigen immobilized on the sensor surface. Immunosensors have following modes:

An indirect (heterogeneous) immunosensor uses a separate named species that is detected after binding either by fluorescence or luminescence,
A direct (homologeneous) immunosensor detects binding by a change in potential or current and is a more sensitive approach with fewer problems.

An electrochemical creatinine sensor was developed using an indirect competitive assay method (Benkert et al., 2000a). The sensing electrode had Pt surface covered with a creatinine-modified electrode consolidated into an electrochemical cell. The sample blend of anti-creatinine antibody and anti-IgG (mouse)-GOx conjugate are blended in the cell. The creatinine to be measured contends with the membrane immobilized creatinine for the antigen-binding sites of the conjugated anticreatine antibodies. Following a washing step, glucose is added and the H_2O_2 produced is measured amperometrically. It is proposed that the membrane reduces unspecific binding of antibodies or redox-active proteins keeping any undesirable reactions at the electrode. The sensor can quantify in the range, 0.09–90 μM with a lower LOD of 40 nM, the lowest LOD for a creatinine sensor. This high sensitivity is profitable for not just low levels of creatinine as well as profoundly weakened or restricted volume sample, e.g. from infants or blood taken from a capillary. However, one measurement cycle takes 30 min adjustment bend information for higher focuses are not accessible. The group later reported on a homogeneous immunosensor based on a size exclusion redox labeled immunoassay that demonstrated a better analytical range of 0.09–900 μM (Benkert et al., 2000b). In this method, creatinine from the sample and engineered redox-labeled creatinine vies for the antigen binding sites of the anticreatinine antibodies. Redox-labeled creatinine not adsorbed by the antibodies, goes through the cellulose membrane to the glassy carbon electrode (GCE). The redox label is a quinine subsidiary that is electrochemically interfere free working similar to counterfeit prescriptions utilized with enzymes. If the creatinine

concentration is high in the sample, the signal response caused by unbound redox-labeled creatinine would likewise be high. The creatinine immunosensors required no recovery and showed an adequate range and sensitivity but these immunosensors ate up a great deal of exorbitant antagonistic to creatinine antibodies.

3.3.1. Merits

Highly sensitivity, low-interference, low cost and compatable with microfabrication technology.

3.3.2. Demerits

Requirement of large amount of expensive anti-creatinine antibodies.

3.4. Enzymeless/chemical creatinine sensors

Enzymeless electrochemical creatinine sensors based on different principles were developed as follow.

3.4.1. Capactive creatinine sensor based on a photografted molecularly imprinted polymer

The molecularly imprinted polymers (MIPs) are a basic and elegant method for embedding recognition sites that have the specificity of antibodies and enzymes in synthetic polymers for the preparation of chemosensors. A capactive creatinine chemosensor is based on the photo-polymerization of the monomer actylamidomethyl propanesulfonic acid and the cross-linker methylenediacrylamide to make a counterfeit receptor layer (Panasyuk-Delaney et al., 2002). A vision electrode surface was altered with a self assembled monolayer of alkane thiol by adsorption of a photo initiator the monomer, the cross-linker and template (creatinine). The treatment with UV radiation developed an ultrathin polymer layer. Removal of the format yielded an electrode surface that was sensitive to creatinine. The molecular imprinting involved the polymerization of functional monomers in the presence of template molecules and initiators. After polymerization, the format molecules were expelled, leaving sites with induced molecular memory that were capable of recognizing the print molecules. The binding of creatinine was recognized by a decrease in the electrode capacitance. The sensor was reversible and exceedingly specific, as no response to expansion of creatinine, urea and glucose was observed.

Another sensor was based on a new MIP for creatinine using screen-printed gold electrodes (Au-SPE). A carboxylic polyvinyl chloride (PVC-COOH) layer was first deposited on Au-SPE surface. The creatinine molecules were attached to the surface of Au-SPE/PVC-COOH. Afterward, the polymerization of acrylamide and N, N′ methylenebisacrylamide filled vacant spaces around them. The subsequent templates removal left binding sites within the polymer, which were capable of selectively recognizing creatinine at different concentrations. To test the sensitivity of this sensor, same procedure without creatinine was performed on a gold non-imprinted polymer (Au-SPE/NIP). Their retention and molecular-recognition properties were qualitatively investigated by means of three instrumental techniques: cyclic voltammetry (CV) and differential pulse voltammetry (DPV), electrochemical impedance spectroscopy (EIS), and UV–Visible spectrophotometry (UV–Vis). The study showed that the MIP had specific recognition ability for creatinine, while other structurally related compounds, such as urea or glucose, could not be recognized on the MIP. In addition, the biosensor was tested on volunteers with different urinary creatinine levels and seemed a promising tool for screening creatinine in point-of-care (POC). Moreover, partial least square (PLS) analysis was used to obtain a correlation between the predicted creatinine concentrations from voltammetric measurements and concentrations measured by Jaffe's reaction as a reference method. The EIS and DPV biosensor responses showed a LOD of 0.016 ng/mL and 0.081 ng/mL respectively, with a linear range from 0.1 ng/mL to 1 μg/mL. This study provided a promising strategy to fabricate sensor devices based on MIP with highly selective recognition ability, simplicity of operation, small size and low cost (Diouf et al., 2017).

3.4.2. Creatinine sensor based on voltammetric behavior of creatinine at phosphomolybdic polypyrrole film modified electrode

The electrochemical conduct of creatinine was contemplated by utilizing Keggin type phosphomolybdate (PMo_{12})-doped polypyrrole (PPy) film modified GCE ($PM0_{12}$-PPy/GCE) (Guo and Guo, 2005). The modified electrode was studied by recording electrochemical behavior of creatinine at 0.5 order differential voltammetry. Creatinine had high inhibitory movement towards the reduction of the adjusted electrode in 0.5 M H_2SO_4, 0.5 order differential voltammetry technology offered incredible favorable circumstances due to fast, simple, high sensitivity, low cost and employed to the monitor the inhibitory movement towards the PMo_{12}–Ppy/GC electrode process.

3.4.3. Creatinine sensor for selective determination of creatinine based on preanodized carbon SPE

An enzymeless electrochemical approach, received from the Jaffe's reaction was developed for specific and quantitative recognition of creatinine in human urine using a preanodized carbon screen printed electrode (SPE) (Chen et al., 2006). The electrode and the active methylene group in creatinine formed a stable selective carbon-carbon bond in the presence of chloride ions. The creatinine was measured by square-wave voltammetry in PBS saline at pH 6.7.

3.4.4. Electrochemical creatinine sensor based on MIPs

An enzymeless electrochemical sensors based on MIPs was fabricated for specific assurance of creatinine, using solvent-evaporation processing of poly (ethylene-co-vinyl alcohol) (EVAL) to form the MIPs (Khadro et al., 2010). The proportion of ethylene and vinyl alcohol for the EVAL is determined in order to obtain higher sensitivity in detection. The carbonyl functions are assigned on the confirmed spectra on removal (after rinsing with 20 mL of ethanol) of format molecule.

3.4.5. Enzymeless creatinine sensor based on poly (3,4-ethylenedioxythiophene)-β-cyclodextrin

Recently, enzyme-less ways utilizing neutral carriers, for example, cyclodextrin and crown ethers, as ionophores for sensing biologically essential molecules have received huge attention. The cyclodextrins are the basket-shaped cyclic glucopyranose oligomer molecules with a hydrophobic inner cavity and hydrophilic exterior. The cyclodextrins have the ability to form inclusion complexes with guest molecules of suitable size through non-covalent interactions, e.g. hydrogen bonding, electrostatic and van der Waals forces. The complexing capacity of cyclodextrin with some biologically vital organic and neutral molecules empowers detecting of these molecules through host–visitors chemistry by potentiometry.

Another novel enzymeless creatinine biosensor using β-cyclodextrin (β-CD)-incorported poly-3,4-ethylenedioxythiophene (PEDOT)-modified GCE was reported (Kumar et al., 2011). The molecular recognition interaction between β-CD and creatinine occurs via weak non-covalent interactions between amide hydrogen of creatinine and glucopyranose oxygen atom in the β-CD. A complex formed between β-CD and creatinine was construed from consistent moves in the electrode potential versus creatinine concentration. The particular interactions of the β-CD-incorported PEDOT film with creatinine in neutral Tris buffer solutions were elucidated using electrochemical-impedance analysis.

3.4.5.1. Merits. Suitable for routine urine analysis, allow either identifying different urine samples or detecting several parameters.

3.4.5.2. Demerits. Complicated and requirement of less recognition locales.

Table 4
A comparison of analytical properties of enzymeless electrochemical creatinine sensor.

Sr no.	Electrodes	Method of detection	Detection limit (μM)	Linear range (μM)	Response time (s)	Interfering compounds	Storage stability (Days)	Samples used	Ref.
1	MIP modified Au electrode	Impedometric	10	50–600	120	No interference	180	Urine	Chen et al. (2006)
2	Phosphomolybdic polypyrrole film modified glassy carbon	Cyclic voltammetry	0.005	1–100	–	–	7	Serum	Hassan et al. (2005)
3	Screen-printed carbon	Square wave voltammetry	8.6	370–3600	–	–	–	Serum	Yadav et al. (2011a,b,c)
4	Metallic electrode/ion selective electrode	Potentiometric	–	–	–	–	–	–	Kozitsina et al. (2009)
5	Organic nickel (II) complex modified GCE	Chronoamperometry	27	50–1000	70	–	–	–	Khadro et al. (2010)
6	Poly (ethylene-co-vinyl alcohol) modified Au electrode	Electrochemical impedance	–	0.44–17.6	20	–	–	–	Kumar et al. (2011)
7	B-cyclodextrin incorporated poly-3,4-ethylene dioxythiophene mofified glassy carbon electrode	Potentiometric	50	100–100,000	60	Ascorbic acid, Uric acid	–	Urine	Chen and Lin (2012)
8	Copper platinum electrode	Cyclic voltammetry	0.5	1.8–108	–	Uric acid	–	–	Carrara et al. (2005)
9	Poly(ethyleneimine)/phosphor-tungstic modified copper (II) ions	Cyclic voltammetry	0.06	0.125–62.5	–	–	–	–	Kasap et al. (2017)
10	Reduced grapheme oxide/AgNPs	Potentiodyanamic	0.0000743	0.00010 − 0.00012	–	No interference	50	Urine	Sittiwong and Unob (2015)
11	AgNPs/polyoxometalate modified GC electrode	Cyclic voltammetry	0.0000151	0.00005–0.0015	–	–	–	Wine, Grapes juice	Zhang et al. (2018)

Abbreviations: MIP = molecularly-imprinted polymer, o-NPOE 0Nitrophenyl octyl ether, DOP dioctylphthalate.
Creatinine acceptor: hybrid film, Signal receptor: working electrode.

3.4.6. A novel structure-specific creatinine sensors

A highly structure-dependent amperometric scheme was developed for assurance of creatinine without enzymes (Chen and Lin, 2012). The principle of this novel method was depended on the development of a dissolvable copper-creatinine complex on the copper electrode surface. Thus, an oxidative current regenerated from the surface-oxide layer was proportional to the concentration of the creatinine. The selectivity and sensitivity of this novel method depends on the chelating ability of creatinine and the copper layers complex rather than the redox behavior of creatinine itself.

3.4.6.1. Merits. Suitable for routine urine analysis even in small quantity.

3.4.6.2. Demerits. Complicated and have less recognition sites.

The analytical properties of enzymeless electrochemical creatinine sensors are shown in Table 4.

3.4.7. Disposable non-enzymatic electrochemical sensor

A disposable non-enzymatic sensor for creatinine was developed by electrodepositing copper on screen printed carbon electrodes. The sensor was characterized utilizing electrochemical and microscopic techniques. Electrochemical detection of creatinine was done in phosphate buffer, pH 7.4. The determination depended on the formation of soluble copper-creatinine complex. The formation of copper-creatinine complex was built up utilizing the pseudoperoxidase activity of copper-creatinine complex. The sensor showed a linear range of 6–378μM with a detection limit of 0.0746 μM. The sensor showed a stable response to creatinine and observed to be free from interference from molecules like urea, glucose, ascorbic acid and dopamine. Real sample analysis was carried out using blood sera (Raveendran et al., 2017). The sensitivity of a biosensor relied upon many components, such as physical design, activity of enzyme, surface activity of the working electrode, inner polymer membranes (covering the surface of the working electrode) that are utilized to immobilize enzymes or to eliminate interference and presence of an outer membrane required to alleviate oxygen dependence and/or to prevent biofouling. The surface activities of these working electrodes were enhanced by altering the working electrodes with NPs. The essential objective of nanomaterials was to expand the surface area of the working electrode however these nanomaterials likewise substantially enhanced electrocatalytic activity, due to a large number of quinoid moieties at the tips of the nanotubes. These biosensors likewise indicated lower response time than non-NP-based biosensors based on cellulose acetate (20 s) (Tsuchida and Yoda, 1983), polypyrrole doped with sulfonated phenoxy resin (100 s) (Yamato et al., 1995), poly-2-hydroxyethyl methyacrylate (300 s) (Madaras and Buck, 1996), poly(1,3-diaminobenzene) (60 s) (Madaras et al., 1996), poly (carbamoyl) sulfonate-hydrogel matrix (20 s) (Schneider et al., 1996), CPE containing 10% Pt power (90 s) (Kim et al., 1999), polyvinyl alcohol (104 s) (Choi et al., 2002), and CPE (30 s) (Stefan et al., 2003). The study showed that NPs enhanced the performance of electrochemical creatinine biosensors (Fig. 5).

3.4.8. Voltammetric creatinine biosensor based on AgNPs/polyoxometalate/GC modified electrode

An enzymeless electrochemical sensor based on MIPs was fabricated for specific assurance of creatinine, using silver nanoparticles (AgNPs)/polyoxometalate functionalized reduced graphene oxide (rGO) coated glassy carbon electrode (GCE) based molecular imprinted voltammetric biosensor (Zhang et al., 2018). This MIP biosensor showed high sensitivity for the detection of creatinine, with LOD as 1.51×10^{-11} M.

3.5. Nanomaterial-based electrochemical creatinine biosensors

Compared to commercial biosensors, nanomaterial-based electrochemical creatinine biosensors have marked advantages, e.g. specificity

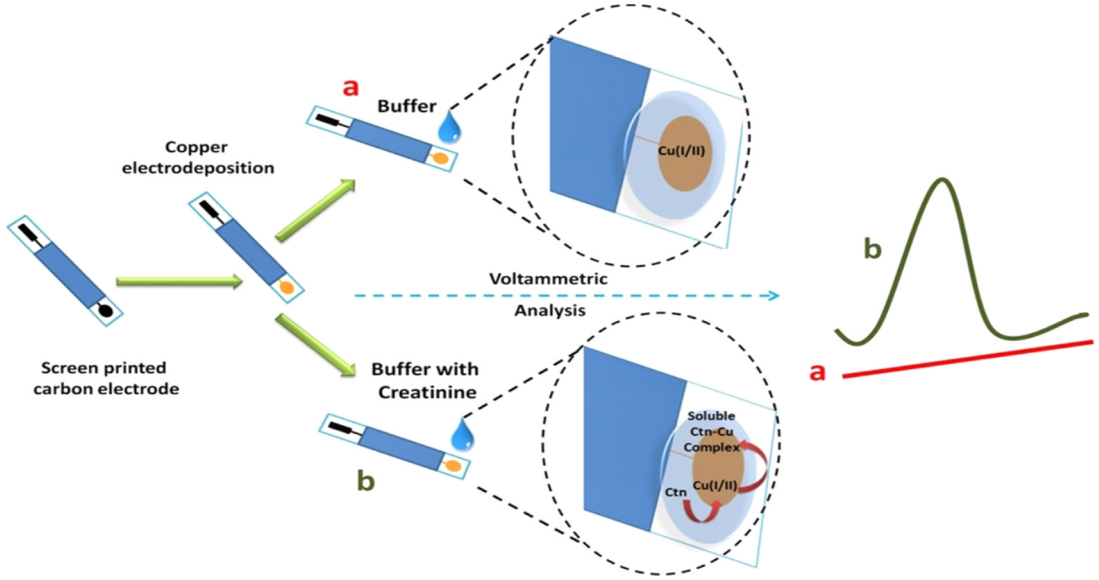

Fig. 5. A disposable non-enzymatic, electrochemical creatinine sensor based on the electrodeposition/copper/screen printed carbon electrodes (Raveendran et al., 2017).

and improved detection sensitivity with great potential for applications in diseased persons (Pundir, 2015). Nanomaterials, especially nanoparticles (NPs) give a promising approach to expand the bio-recognition area, because the high surface area to volume ratio of NPs makes a larger number of sites available for molecular interactions. Researchers have tendency to integrate NPs into the materials used for biosensor construction in order to improve the performance of the system in existing and potential sensing applications. The recent constructions of enzymatic creatinine biosensors in view of different NPs such as carbon nanotubes (CNTs), ZnO and Fe_3O_4 NPs are discussed below. The different NPs-based creatinine biosensors developed so far and their sensitivity, LOD, response time and applied potential are highlighted in Table 5.

3.5.1. Carboxylated multi-walled CNTs based creatinine biosensor

The excellence of CNTs like, large surface area, favorable electronic properties and electrocatalytic effect have very recently attracted considerable attention for the construction of electrochemical enzyme biosensors. This configuration guarantees an augmented zone for immobilization of biomolecules. Adding, conducting polymers to CNTs decrease charge transfer resistance and mass exchange impedance to a more extent than different nanomaterials (Carrara et al., 2005). An amperometric creatinine biosensor was developed by co-immobilizing covalently CA, CI, SOx via N-ethyl-N-(3-dimethylaminopropyl) carbodimide (EDC) and N-hydroxy succinimide (NHS) chemistry, onto a carboxylated MWCNT (c-MWCNT)/polyaniline (PANI) nanocomposite film electrodeposited over the surface of a platinum (Pt) electrode. The creatinine biosensor showed optimum response within 5 s at 0.2 V, pH 7.5 and temp 35 °C with a lower detection limit of 0.1 μM and linearity in concentration range of 10–750 μM creatinine. The biosensor had a sensitivity of 0.040 μA/μM/cm^2 and an apparent Michaelis-Menten constant (App Km) of 0.26 mM. The biosensor had a high storage stability has maintaining 85% of the initial current response even following 180 days of regular use (150 times) (Yadav et al., 2011a,b,c).

3.5.2. Zinc-oxide NPs and c-MWCNTs based creatinine biosensor

Our group synthesized zinc-oxide NP/chitosan/c-MWCNT/polyaniline (ZnO-NPs/CHIT/c-MWCNT/PANI) composite film on a Pt electrode for construction of a creatinine biosensor (Fig. 6) (Yadav et al., 2011a,b,c). c-MWCNTs in a suspension individually could be cytotoxic but cytotoxicity was avoided by immobilization of c-MWCNTs on a surface or within a composite (Hussain et al., 2009). The addition of NPs to c-MWCNT films could generate new nanostructure with great behavior in optics, electronics and electrocatalysis (Wang et al., 2007). Metal NP-modified electrodes had unusual advantages in electroanalysis such as improved electronalysis, due to enhanced catalysis of electron transport large effective surface area and control over the electrode microenvironment (Luo et al., 2004; Singh et al., 2007). The enzymes CA, CI, and SOx were immobilized on the ZnO-NP/CHIT/c-MWCNT/PANI composite film-modified electrode. This enzyme electrode detected creatinine levels as low as 0.5 μM within 10 s at pH 7.5 and 30 °C when polarized at 0.5 V versus Ag/AgCl. The creatinine biosensor had a working range of 10–650 μM for creatinine with a sensitivity of 0.030 μA/μM/cm^2. The biosensor lost 15% of its initial activity over a period of 120 days, when stored dry at 4 °C. The app K_m was 0.35 mM (Welch and Compton, 2006).

3.5.3. Iron-oxide NPs based creatinine biosensor

An amperometric creatinine biosensor was fabricated by co-immobilizing CA, CI and SOx covalently onto iron-oxide NP/chitosan-graft-polyaniline (Fe_3O_4–NP/CHIT-g-PANI) composite film (Pundir et al., 2013). However, Fe_3O_4–NPs were interfering for the immobilization of target biomolecules, because of their biocompatibility and their solid superparamagnetic behavior, which gave better contact and low lethality (Gupta and Gupta, 2005). Immobilization of such bioactive molecules onto a surface charged with superparamagnetic NPs was of special interest, since the magnetic behavior of these bioconjugates resulted in enhanced delivery and recovery of biomolecules for desirable biosensing applications (Rossi et al., 2004; Kouassi et al., 2005; Kaushik et al., 2008). The biosensor showed an optimum response within 2 s at pH 7.5 and 30 °C when polarized at 0.4 V versus Ag/AgCl. The electrocatalytic response was linear for creatinine in the concentration range 1–800 μM. The sensitivity of the biosensor was 3.9 μA/μM/cm^2 with a LOD of 1 μM (S/N = 3). The apparent K_m value for creatinine was 0.17 mM. The biosensor lost 10% of its initial response after 120 uses more than 200 days, when stored dry at 4 °C.

Nano-materials have desirable properties, e.g. large surface-to-volume ratio, high surface reaction activity, high catalytic efficiency and

Table 5
A comparison of analytical properties of nanopmaterials based amperometric creatinine biosensors.

Sr no.	Support for immobilization	Enzymes	Working electrode	Method of immobilization	Optimum pH	Detection limit (μM)	Linear range (μM)	Response time (s)	Sensitivity (μA/μM/cm^2)	Potential applied	Interfering compounds	Storage stability (days)	Samples used	Ref.
1	c-MWCNT/ PANI	CA, CI, SOx	Pt	Covalent	7.6	0.1	10–750	5	0.040	0.2	No interference	180	Serum	Yadav et al. (2011a,b,c)
2	ZnO-NPs/CHIT/ c-MWCNT/ PANI	CA, CI, SOx	Pt	Covalent	7.5	0.5	10–650	10	0.030	0.5	Creatine	12	do	Yadav et al. (2012)
3	FeO_4 –NPs/CHIT-g-PANI	CA, CI, SOx	Pt	Covalent	7.5	1	1–800	2	3.9	0.4	Creatine, sarcosine	200	do	Marchenko et al. (2015)
4	Fe_3O_4	CI, SOx	Carbon paste electrode	Adsorption	7.0	0.2	1–38	10	–	0.3	Ascorbic acid, Uric acid	30	–	Shaidarova et al. (2014)
5	Au NPs	CA	GC	Adsorption	–	5.1	5.1–5100	–	–	–	–	–	–	Osman et al. (2013)
6	$Hg(2^+)$	CA	Au NPs	Cross-linking	–	–	–	–	–	–	–	–	Urine	Sutariyaa et al. (2016)
7.	Calyx[4]arene	CA	Au NPs	Covalent	–	–	–	60	–	–	–	35	Urine, Serum, Post-themo-dialysate	Radomska (2004)
8	–	CA	ISFET	Cross-linking	7.4	–	–	–	–	–	–	–	Serum, Urine	Viswanath et al. (2017)
9	AuNPs	CA	Sulfonic acid funtionalized silica gel	–	–	13.7	15–40	–	–	–	No interference	–	–	Zhybak et al. (2016)
10	–	CA, CI, SOx	GC	Adsorption	6.0	0.01	0.01–12	2	–	1.0	No interference	240	Serum	Kumar et al. (2017)

Abbreviations: CA creatinine amidohydrolase, CI creatine amidinohydrolase, SOx sarcosine oxidase, c-MWCNT carboxylated multiwalled carbon nanotubes, PANI polyaniline, ZnO-NP zinic oxide nanoparticle, CHIT chitosan, FeO_4-NP iron oxide nanopaticle, CHIT-g-PANI chitosan grafted polyaniline, GC glassy carbon electrode.
Creatinine acceptor: CA NPs, Signal receptor: working electrode.
Working mechanism: .

a)
$$\text{CA, CI, SOx} = \text{Creatinine} + H_2O \xrightarrow{CA} \text{Creatinine}$$
$$\text{Creatine} + H_2O \xrightarrow{CI} \text{Urea} + \text{Sarcosine}$$
$$\text{Sarcosine} + O_2 + H_2O \xrightarrow{SOx} \text{Glycine} + HCHO + H_2O_2$$

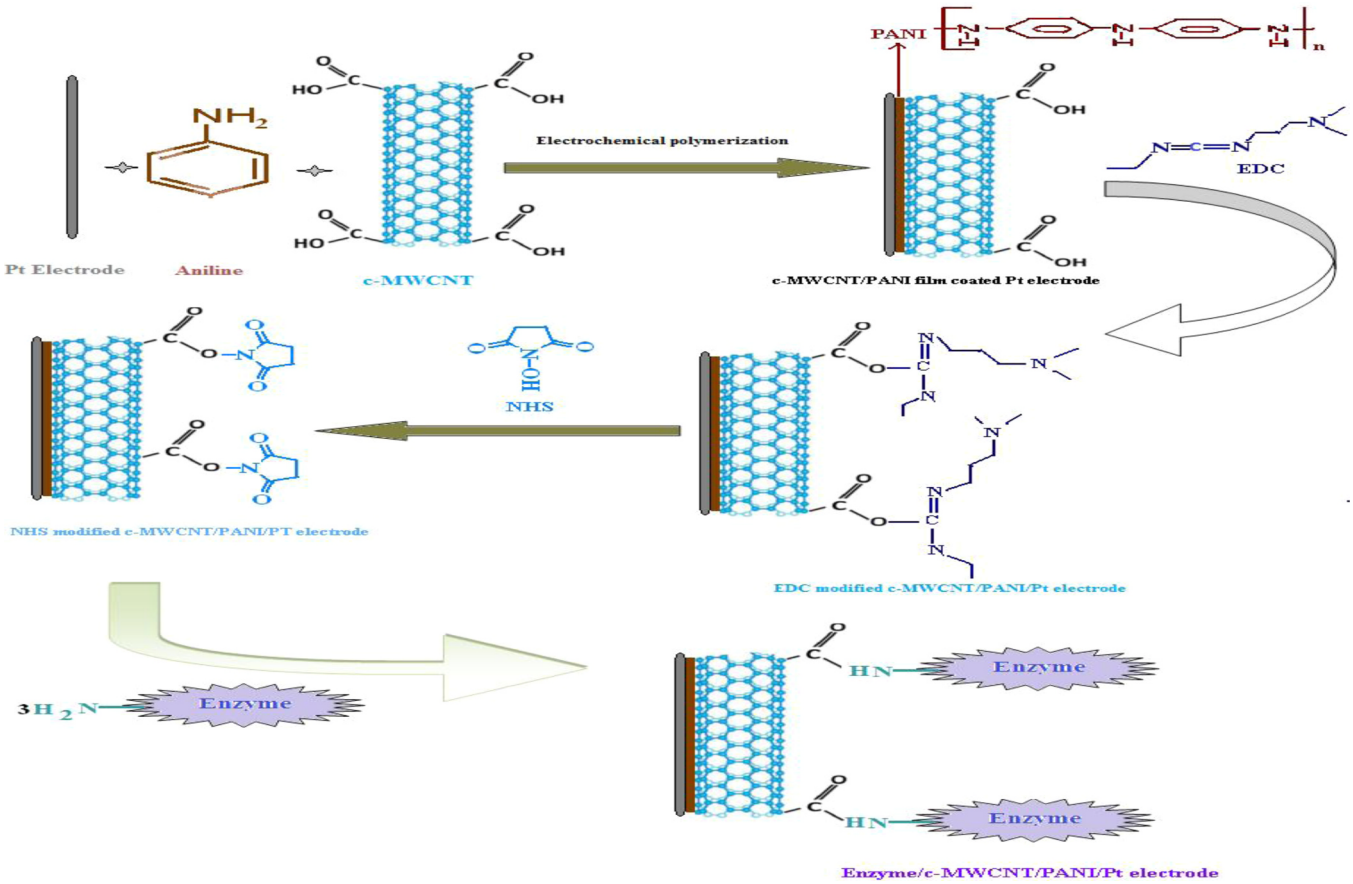

Fig. 6. Schematic representation of chemical reaction involved in the fabrication of Enzymes/c-MWCNT/PANI/Pt hybrid electrode (Yadav et al., 2011a,b,c).

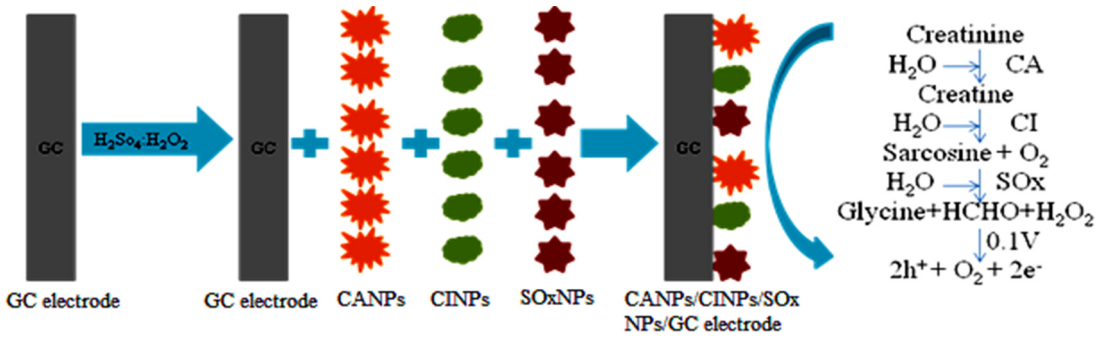

Fig. 7. Schematic representation of fabrication of CANPs/CINPs/SOxNPs/GC electrode (Kumar et al., 2017).

strong adsorption ability that are useful in biosensing applications. Nanomaterials have one of the kind capacities of promoting fast electron transfer between electrode and the active site of the enzyme. Among them, magnetite nanoparticles have increased much attention because of biocompatibility, lower mass transfer resistance, strong superparamagnetic property and low toxicity. Fe_3O_4-nanoparticles-based amperometric biosensor for creatine determination exhibited an optimum response, pH, working potential, enzyme loading as 7.0, 0.30 V and 2.0U (CI), 1.0U (SOx), respectively. The biosensor exhibited linear response from 2.0×10^{-7} mol L^{-1} to 3.8×10^{-6} mol L^{-1} and from 9.0×10^{-6} mol L^{-1} to 1.2×10^{-4} mol L^{-1} with a detection limit of 2.0×10^{-7} mol L^{-1}. Biosensor was used for determination of creatine in commercial creatine powder samples and showed a good sensing performance (Kaçar et al., 2013).

These NPs-based amperometric creatinine biosensors have shown enhanced performance e.g., sensitivity, response time, accuracy biocompatibility and stability. The NP-based creatinine biosensor exhibited lower app K_m than that of a non-NP-based microfabricated creatinine biosensor (5.2 mM) (Madaras et al., 1996) and a CPE-based creatinine biosensor (5.15 mM) (Kim et al., 1999). The low app K_m indicated that the enzymes immobilized onto c-MWCNT/PANI, ZnONPs/CHIT/c-MWCNT/PANI and FeO_4-NPs/CHIT-g-PANI composites films kept their activity with a very low diffusion barrier. This was a great advantage over other composites, since the NPs maintain the conducting properties and allow easy, fast incorporation of the enzyme with a very low app K_m and high sensitivity. The sensitivity of these biosensors was higher than non-NP-based creatinine biosensor based on controlled pore glass (0.0000208 μA/μM/cm^2) (Sakslund and Hammerich, 1992), poly-2-hydroxyethyl methyacrylate (0.0000139 μA/μM/cm^2) (Madaras et al., 1996), gas permeable membrane (0.000001 μA/μM/cm^2) (Osborne and Girault, 1995), poly (carbamoyl) sulfonate-hydrogel with Nafion (0.005 μA/μM/cm^2) (Shin et al., 2001), polyvinyl alcohol (0.0001256 μA/μM/cm^2) (Choi et al., 2002), and poly (carbamoyl) sulfonate-hydrogel matrix (0.00024–0.00046 μA/μM/cm^2) (Suzuki and Matsugi, 2005).

3.6. Enzyme nanoparticles (ENPs) based biosensor

In creatinine biosensors, the enzymes were immobilized onto different nanocomposites, for detection of creatinine in biological fluids. However, direct immobilization of enzymes onto nanocomposites may realize their denaturation, leading to the loss of their activity and stability. The issue was defeated utilizing enzyme nanoparticles (ENPs) instead of native enzyme molecules. ENPs are the aggregates of enzyme molecules in the nanoscale, which show their exceptional physiochemical properties. Due to their unique electronic, optical, mechanical, electrical, thermal and catalytic (ability to facilitate electron transfer) properties, beside the increasing surface area, ENPs have demonstrated extraordinary promises an enhancing electrodes. Accordingly, the use of ENPs rather than native enzyme in construction of amperometric biosensor has not only improved the analytic performance of biosensor but also simplified the construction of enzyme electrode (Pundir, 2015). An amperometric creatinine biosensor was fabricated by immobilizing ENPs of CA, CI and SOx onto glassy carbon (GC) electrode for improved amperometric determination of creatinine in blood. The biosensor exhibited optimum current at 0.4 V, within 10 s, at pH 7.25, 34 °C, with LOD as 50 μM and working range from 50 to 1000 μM. The electrode worked upto 30 days during its regular uses, when stored at 4 °C (Busono et al., 2015). An improved amperometric creatinine biosensor was designed in our laboratory by immobilizing of ENPs of CA, CI and SOx onto glassy carbon electrode (GCE). The modified GCE showed good conductivity, ultra low cost, low background current and easy availability, which made it a better option over electrodes such as Au, carbon and silicalite electrodes. This ENPs/GCE based biosensor showed optimum response at 0.1 V against Ag/AgCl, within 2 s at a pH 6.0 and 25 °C. The ENPs/GC electrode showed lower LOD (0.01 μM) and good correlation coefficient (R^2 = 0.99) with a standard enzymic colorimetric method. The analytical recovery of added creatine in serum (0.1 and 0.15 mM) was 97.97 ± 0.1% and 98.76 ± 0.2% respectively, within and between batch CV were 2.06% and 3.09%. The biosensor measured creatinine in the serum of apparently healthy subject and persons suffering from renal disorder. The ENPs modified electrode lost only 10% of its initial activity after its continued uses over a period of 240 days, while being stored at 4 °C (Kumar et al., 2017) (Fig. 7).

4. Summary and conclusion

In conclusion, biosensing methods are comparatively better than traditional methods such as colorimetric, enzymic colorimetric, spectrophotometric and chromatographic methods for quantitative determination of creatinine. Biosensor technology emerges as more refined and reliable, as its goal is to provide simple, ultra sensitive, selective and, disposable analytic device, which works with complete automation and provides rapid response. The creatinine sensors/biosensors reported so far, have worked ideally within 2–900s, working potential 0.1–1.0 V, in the pH range, 4.0–10.0, temperature range 25–35 °C and linear range, 0.004–30,000μM, with the detection limits between 0.01 and 520 μM. These biosensors measured creatinine level in sera and urine samples and had storage stability of 4–300 days, while stored dry at 4 °C. The direct immobilization of enzyme nanoparticles in place of native enzyme(s) in creatinine biosensor has not only improved its analytic performance but also simplified its fabrication process (Kumar et al., 2017).

5. Future perspective

The use of paper analytical devises (PAD) in portable biosensors has attracted the attention of diagnostic industry. The electrochemical PADs (ePADs) are not only disposable but also provide simplicity, low cost, mass production, detection with minimal quantity of analyte, low limit of detection and low power requirements. Hence, ePADs work as an ideal platform for diagnostic tools (Singhal et al., 2018; Yadav et al., 2018). However, there is no report on ePADs for detection of creatinine. The future research could be focused to design electronic chip and lab on paper chip to develop a fully automatic portable device, which can be used by the patients at his/her bedside. Labs on chip devices present many advantageous features such as minimal sample requirement, non-tedious and facile approach, cost-effective lab on a chip and fast response. The captivating features of paper based devices would make it highly suitable for determination of various metabolites, in biological fluids.

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