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Review

Determination of Caffeine: A Comprehensive Review on Electrochemical Methods

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Caffeine is a psychoactive substance in daily human life which plays an important role in food and drug chemistry. The beverages such as coffee, tea, cola or drug formulations belong to the significant economic products in which the highest quality in international business is demanded. In respect to an ascending number of samples, the novel and perspective analytical methods for determination of caffeine providing accurate and reliable results are necessary. Electrochemical methods have been commonly exploited as cheap, rapid and simple alternatives to modern separation and spectral methods. To-date however, a comprehensive review on the electrochemical determination of caffeine has not been reported. Herein the present paper gives a summary on the current state in this field. The major part deals with the use of bare and modified carbon-based electrodes as voltammetric sensors for determination of caffeine. Amperometric, potentiometric and piezoelectric methods are also discussed in this review.

Keywords: Caffeine, Carbon-based electrode, Detection limit, Modified electrode, Voltammetry

1. INTRODUCTION

Caffeine (IUPAC name: 3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione) is a natural alkaloid belonging to *N*-methyl derivatives of xanthine. Because of high popularity of coffee and other caffeine containing products (coca, tea, soft and energy drinks, cocoa, chocolate), it is the most commonly used psychoactive substance in daily human life. Caffeine (CAF) is also distributed in plants where it serves as a natural insecticide since it may paralyze and kill some insects feeding on the plant [1]. For humans, CAF has many important physiological effects, such as stimulation of the central nervous system, diuresis and gastric acid secretion [2]. However, the high amounts of CAF can cause trembling, nausea, nervousness and seizures [3] and mutation effects such as inhibition of DNA [4]. A

fatal dose of CAF has been evaluated to be more than 10 g (about 170 mg kg^{-1} of body weight). It is also considered to be a risk species for cardiovascular diseases, kidney malfunction and may also cause hyperactivity [5]. CAF is usually prescribed as analgesic adjuvant in drug formulations for the treatment of headache and pain related to postpartum, postoperative, and dental surgery and therapeutically used for the treatment of migraine in combination with other drugs such as aspirin (ASP), paracetamol (PAR), ascorbic acid (AA) [6]. Many contributions dealing with impact studies of CAF on human health have been reported in last years [7-11].

CAF is very attractive compounds for analytical chemists, thus its beverages (various type of coffee, tea, cola, cocoa, energy drinks) and drug formulations belong to the significant economic products in which the highest quality in international business is demanded [12]. Owing to its common use, the eventual abuse, the important effects in human system and in respect to the ascending number of samples, the novel and perspective analytical methods providing rapid, sensitive and reliable detection and determination of CAF are still necessary. It is always needful to find such method which is the most appropriate for particular purpose (determination of CAF in specific matrix, in the presence of interfering agents as well as specific concentration range under the minimal elaborateness, the lowest economic and time difficulties) [13]. Moreover, with respect to the above mentioned facts the detection and quantification of CAF is important from analytical point of view and does not have the significance only in food and drug chemistry, but it can also give beneficial advice to people's health and life. Numerous studies aimed towards the development of analytical methods for determination of CAF in different matrix (beverage, food, environmental, biological etc.) have been published.

Nowadays, massive majority of analytical society inheres in a decade of separation methods and hyphenated techniques, interfaced with mass spectrometry or other spectral techniques. Regarding the determination of CAF, many modern separation methods with excellent sensitivity, selectivity and detection limit for CAF usually lower than 10^{-8} M such as gas chromatography with mass spectrometry [14-16], liquid chromatography with mass spectrometry [17] as well as diode array detector [18-20] are mostly dominating in analytical laboratories. However, most of these methods are prone to many drawbacks, such as expensiveness, lengthy and complicated sample pretreatment usually involving preconcentration step such as derivatization and various types of extraction (solid phase extraction, solid phase microextraction, liquid-liquid extraction) prior to the analysis [21,22]. Besides, the demands for highly skilled personnel often restrict their use in routine analytical practice.

Spectral methods are often used in analytical laboratories in the context of determination of CAF. Generally, the principal reasons for their popularity are easy availability of photomers, colorimeters or single beam spectrophotometers. Most of such methods involves molecular absorption spectroscopy in the ultraviolet and visible region [23-25], infrared spectroscopy with Fourier transformation [26,27] and nuclear magnetic resonation [28]. The disadvantages of spectral methods consist in time-consuming and complicated sample preparation as well as oftentimes lower sensitivity of analysis without preconcentration step.

Electrochemical methods offer the practical advantages including operation simplicity, satisfactory sensitivity, wide linear concentration range, low expense of instrument, possibility of miniaturization, suitability for real-time detection and less sensitivity to matrix effects in comparison with separation and spectral methods [29-31]. Due to their higher sensitivity and low detection limits,

the electroanalytical methods based on stripping processes are useful and popular in trace analysis [32].

Electrochemical methodologies for the determination of CAF on different electrode materials (usually bare and miscellaneously modified carbon-based electrodes) are summarized and reviewed here in detail. From the general knowledge it is important to point out the fact that no official attempts for summary of electroanalysis of CAF have been published until now in accessible literature. Thus, the overview of voltammetric, potentiometric, amperometric and piezoelectric sensors for the determination of CAF is provided in following sections and listed with basic characteristics in Tables 1-4.

2. ELECTROCHEMICAL METHODS

Generally a few years ago, the electrochemical methods have rarely been used for the determination of CAF. The major drawback embodies in the use of conventional bare electrode materials (e.g. glassy carbon, graphite, carbon paste) at which the oxidation of CAF occurs at a very positive potential (usually more than +1.3 V *vs*. Ag/AgCl electrode). Thus, the determination may be limited by usable potential range of electrode material or overlapping with the potential of discharged electrolytic solution in anodic side often leading to low reproducible results [33-35]. This fact must be taken into account by electrochemists in the optimation of experimental conditions (selection of appropriate working electrode material and supporting electrolyte). In order to avoid the overlapping of the oxidation peak of CAF with the electrolyte, several types of carbon-based electrodes have been examined using electrochemical techniques. Nevertheless, the big growth of published reports dealing with electrochemical determination of CAF was observed in last three years. The main reason consists in the use of miscellaneous modifiers and the exploitation of boron-doped diamond as the versatile electrochemical tools largely improving the sensitivity and selectivity.

The comprehensive summary of the electrochemical determination of CAF from all years is reviewed here in five sections with the greatest emphasis on the voltammetric methods using bare and modified carbon electrodes.

2.1. Voltammetry on bare carbon electrodes

In recent times, the carbon-based electrode materials are nearly ubiquitous in the electrochemical laboratory because of their availability in various forms and shapes, and usefulness over the relatively wide potential range in cathodic and anodic area [36]. The most commonly used carbon-based material in the analytical laboratory known for its chemical stability and relatively large over-potential of oxygen and hydrogen evolutions is glassy carbon electrode (GCE) [37]. The first report dealing with the determination of CAF on GCE without the sample pretreatment was presented by Sontag and Krai [38]. However, the strong adsorption of CAF required the mechanical and electrochemical pretreatment of GCE surface and also the use of tensoactive substances. Consequently

this procedure restrained the use of voltammetry in routine laboratory analysis. The simple, rapid and accurate differential pulse voltammetric (DPV) method for the determination of CAF simultaneously with PAR and AA in drug formulations on GCE was reported by Lau et al. [39]. The authors used an unusual combination of methanol and perchloric acid (1:1) as the solvent and supporting electrolyte to improve the sensitivity and peak separation of CAF and PAR. Obviously, it was difficult to make quantitative determination due to the addition of easily evaporating methanol. Câmpean et al. [40] exploited an electrochemically activated (EA) GCE with anodic pre-treatment at 1.8 V *vs*. Ag/AgCl electrode for the determination of CAF and other alkaloids (aminophylline, theophylline and codeine) in urine and drug formulations.

Carbon paste electrodes (CPEs) prepared by mixing a graphite powder with insulating liquids such as paraffin oil or silicon oil represent one of the most used types of working electrode. They possess the many advantages such as easily renewable surface, low cost and very low background currents especially in the anodic area [41]. One of the disadvantages of CPE is the tendency of organic binder to dissolve in solutions containing organic solvents. Mersal [42] prepared unmodified pseudo carbon paste microelectrode (CPME) by mixing graphite powder with paraffin wax and studied the electrochemical behavior of CAF. This electrode showed the good sensitivity and high selectivity for the direct determination of CAF using square wave voltammetry (SWV).

The use of fast-scan voltammetric (FSV) procedure under physiological conditions for future *in vivo* or biological fluid analysis of CAF on carbon fiber ultramicroelectrode (CFUME) was reported by Nunes and Cavalheiro [43]. The main advantages of the CFUME consist in the capability of operating in a relatively high anodic potential at which CAF is oxidized (allowing the background subtraction), the possibility of sensor construction as well as the speed of the measurements. The unique properties of CFUME make them very attractive in electroanalytical measurements due to increase of signal-to-noise ratios (S/N) arising from the efficient mass transport to the electrode because of edge effects [44]. In addition, the small dimensions of CFUME, low IR drop and fast scan result in voltammetric measurements also in highly resistive media [45].

Ly et al. [46] developed the square-wave voltammetric method in anodic stripping mode (SWASV) using the commercial graphite pencil electrode (GPE) as a viable technique for monitoring of CAF levels in several tea samples. The optimum conditions for stripping process using the GPE were evaluated and the very wide linear concentration range was achieved. The attained results by GPE were comparable with those of the CPE method. Although GPE is the relatively new type of carbon electrode, it is cheaper, more convenient and renewable alternative to the commonly used CPE or GCE. A simple and sensitive electrochemical method for the determination of CAF in coffee, drug formulations and human urine using edge plane pyrolytic graphite electrode (EPPGE) was evolved by Goyal et al. [47]. The excellent reproducibility, the very low detection limit of 0.008 μM and long term stability of EPPGE with essentially no pretreatment and surface modification offer the good possibility for routine analysis of CAF. The use of EPPGE was well established in voltammetric analysis also due to its unique properties such as wide potential range, low background current, high selectivity and sensitivity [48,49]. Moreover, electron transfer rate constants for a large variety of redox couples at EPPGE have been found to be thousand times faster than other conventional electrodes [50].

Boron-doped diamond is one of the novel carbon-based material, which has received much attention in last twenties years [51]. It possesses the various desirable properties, such as high thermal conductivity, low adsorption ability, extreme electrochemical stability in both alkaline and acidic media, very low and stable background current as well as absolutely the widest usable potential range [52,53]. These properties are commonly induced by morphologic factors, crystallographic orientation and presence of impurities (non-diamond sp^2 carbon) which make the bare boron-doped diamond electrode (BDDE) surface significantly different from other conventional carbon-based electrodes, e.g. GCE or CPE. Spătaru et al. [34] studied the oxidation of CAF and characterized the irreversible electrochemical behavior of CAF on bare BDDE using cyclic voltammetry and linear sweep voltammetry (LSV). They proposed the oxidation scheme of CAF which is similar to mechanism according to Dryhurst and Hansen [54] who absolutely as the first authors were dealing with the oxidation of CAF. It can be concluded that overall process involves four electrons ($4e^-$) and four protons ($4H^+$) as depicted in Fig. 1.

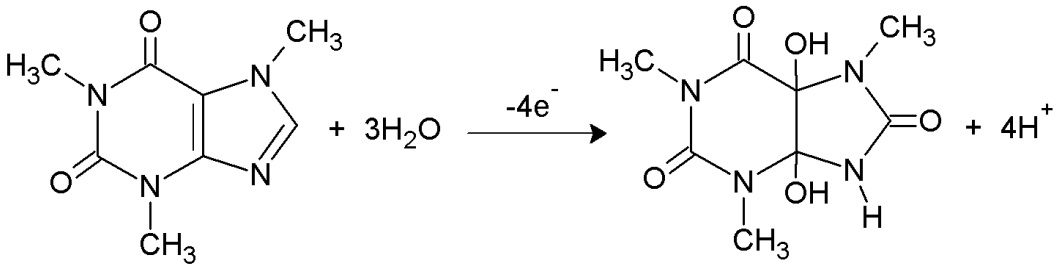

Figure 1. Mechanism of overall oxidation of CAF [34,54]

The first step is a $2e^-$, $2H^+$ oxidation of the C-8 to N-9 bond to give the substituted uric acid, followed by an immediate $2e^-$, $2H^+$ oxidation to the 4,5-diol analogue of uric acid, which rapidly fragmented.

A simple and fast DPV method for simultaneous determination of CAF and acetylsalicylic acid without its alkaline hydrolysis in drug formulations on BDDE was developed by Faria et al. [55]. The proposed method presented the advantages including lower cost in comparison with chromatographic methods, allowing for an analysis with fewer tedious sample preparation steps and less waste. Švorc et al. [56] reported the sensitive and selective determination of CAF using DPV on bare BDDE. The relatively low detection limit of 0.15 μM was obtained as a consequence of high S/N ratio without any modification and electrochemical pretreatment of the BDDE surface. The effect of the presence of theophylline (THO) as the structurally similar compound to CAF usually present in tea was also studied. It is apparent from Fig. 2 that the good peak separation is observed in 10-fold excess of THO. This fact opens promising possibilities for their simultaneous determination on BDDE.

Lourenção et al. used cathodically pre-treated (CP) BDDE for simple and highly selective electrochemical determination of CAF individually and simultaneously with AA [57] and PAR [58] in drug formulations. The good peak separation of about 0.6 (0.5) V between the peak potentials of CAF and AA (PAR) present in binary mixtures was obtained.

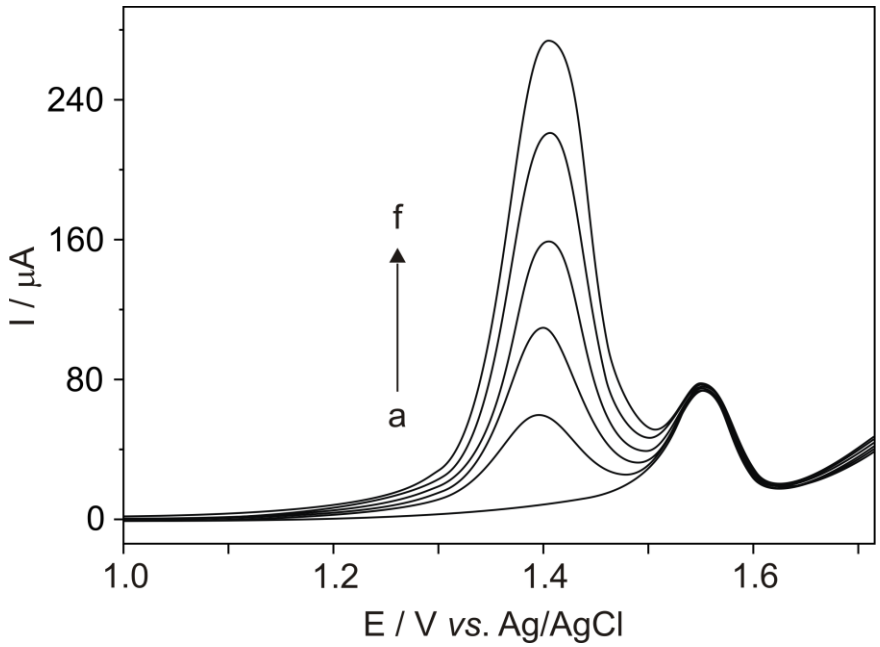

Figure 2. DP voltammograms of 10 μM CAF (fixed concentration) and different THO concentrations: (a) 0, (b) 20, (c) 40, (d) 60, (e) 80 and (f) 100 μM (supporting electrolyte 0.4 M $HClO_4$) on bare BDDE at optimized DPV parameters: modulation amplitude of 0.05 V, modulation time 0.02 s and scan rate 0.05 V s^{-1} [56].

The important point in these papers should be highlighted as the anti-fouling properties of BDDE, which allow the use of this electrode for a long time with the same response.

2.2. Voltammetry on modified carbon electrodes

As it is written previously, the oxidation of CAF occurs at the very positive potential overlapping with the oxidation of the background medium, which gives the analysis the low reproducibility [33-35]. Several solutions including the use of bare electrodes with wide range of polarizability (especially in anodic area as mentioned in detail in section 2.1.) or modified electrodes were proposed. Over the years, many types of modified working electrodes have been developed and used in various ways for voltammetric measurements. In order to enhance the sensitivity and stability of the measurements, the electrodes modified with designable molecules have been used in electrochemical determination of CAF. Although the majority of modified electrodes successfully determined the concentrations of CAF, the fabrication of the electrochemical sensor is still one of the challenging tasks for the researchers.

Nafion, a perfluorosulfonated derivative of Teflon, is a cation-exchange polymer with properties of excellent antifouling capacity, chemical inertness and high permeability to cations. Especially in the last two decades, the researchers have made extensive use of Nafion-modified electrodes for wide variety of electrochemical applications from sensors [59,60] to fuel cells [61]. In particular, the Nafion showed a good affinity towards CAF because of its substantial improvement of sensitivity in acidic conditions [62]. In this case, Brunetti et al. [33] developed a simple DPV method

based on Nafion-modified GCE for the quantitative determination of CAF in cola beverages. The modified electrode exhibited the clear enhancement of the current response in comparison to bare GCE due to incorporation of CAF into the polymer layer, until the equilibrium conditions were achieved (after 10 min). This effect is similar to that employed in stripping voltammetry [63] as for this case it is based on chemical preconcentration step instead of electrochemical one.

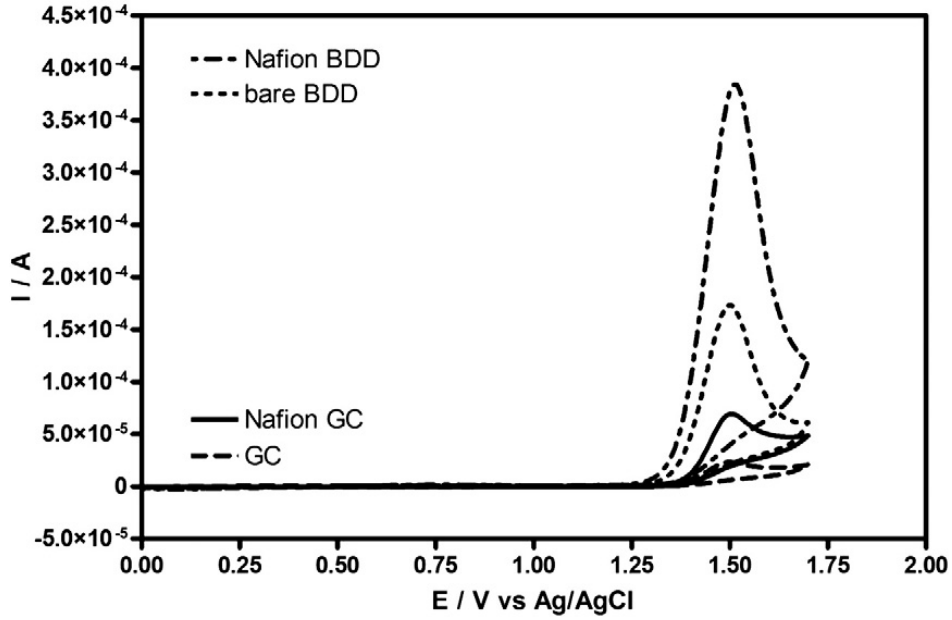

Figure 3. Cyclic voltammograms recorded on bare and Nafion-modified GCE and BDDE; 100 μL of 0.1 M CAF in 30 mL of 0.2 M H_2SO_4 solution (scan rate: 100 mV s^{-1}) [35].

The Nafion-modified BDDE also seems to offer a fast, reliable, economic and simple way for the determination of CAF as reported Martínez-Huitle et al. [35]. This electrochemical sensor was characterized by higher sensitivity and reproducibility than the bare BDDE and bare/modified GCE (Fig. 3), and the low detection limit allows the reducing matrix effects in highly diluted solutions. These results give also an idea about the advantages of using the modified BDDE, with respect to either the Nafion-modified GCE [33] or the CP-BDD electrode [57], especially in relation to the detection limit.

The Nafion–ruthenium oxide pyrochlore (RuOP) chemically modified electrode (CME) was used for the determination of CAF individually in beverages [64] and simultaneously with PAR in drug formulations [65]. The significant advantages as excellent sensitivity and selectivity have been achieved by combining the electrocatalytic function of RuOP catalyst with the charge-exclusion and preconcentration features of Nafion.

Recently, electrochemically polymerized conducting polymers attracted much attention in electroanalytical chemistry. Numerous studies of conducting polymers have been reported [66-68]. Amare and Admassie [69] developed a polymer-modified electrode that lowers the oxidation potential of CAF and enables its determination in coffee without the significant influence from background

current. They used 4-amino-3-hydroxynaphthalene sulfonic acid (AHNSA) as stable electrodeposited film on GCE showing the electrocatalytic activity towards the oxidation of CAF. This modifier is relatively cheaper than other modifiers reported and easily deposited on the electrode surface [33,35,63]. Wang et al. [70] investigated the electrochemical behavior of CAF and THO on a poly(4-aminopyridine)(PAP) modified GCE. This electrode had the advantages of stability, fast response and good reproducibility. The peak separation between CAF and THO was about 0.13 V. The self-assembled monolayer (SAM) of non-peripheral amine substituted copper(II) phthalocyanine (Cu^{II} TAPc) on GCE was prepared and used for the selective determination of CAF in human blood serum and drug formulations in the presence of PAR [71]. This electrochemical sensor did not only shift the oxidation potential of CAF toward less positive one but also enhanced its oxidation current when compared to bare GCE.

The novel, sensitive and stable electrochemical sensor for simultaneous determination of CAF and PAR was fabricated and introduced by Xiong et al. [72]. It was based on electrochemically polymerized taurine (PT) layer on a TiO_2 modified GCE. Being a famous semiconductor, TiO_2 has been received much attention due to its nontoxicity, long-term stability and low cost [73]. Concerning the taurine, there is electron-rich N atom and high electron density of sulfonic groups [74]. Hence, the PT film is negatively charged and is prone to adsorb CAF from the solution. This sensor is ease to construct, low cost and no treatment before use made it feasible to be applied in routine determination. Polysafranine T (PST) film was prepared by the electropolymerisation of safranine T on GCE in order to design the new voltammetric sensor for the sensitive and selective determination of CAF in tea [75]. To avoid the interferences of the anions, Nafion was covered on the surface of PST film modified GCE. The electropolymerised film was uniform, crystallisable and exhibited the strong catalytic effect towards the electro-oxidation of CAF. The method also produced much less organic waste compared with other analytical methods. Aklilu et al. [76] applied 1,4-benzoquinone (BQ) modified CPE for the indirect voltammetric determination of CAF in coffee with the aim of raising the selectivity and sensitivity. The principle was based on decrease of BQ reduction peak current after addition of CAF. The method was fast, simple, sensitive and cost-effective as well as did not require sophisticated equipment.

Carbon nanomaterials such as graphene (GR) and graphene oxide (GO) have attracted the attention increasingly since their discovery in 2004 [77]. They have been widely used in analytical chemistry as chemical sensor and biosensor materials due to their thermal and mechanical properties, high electrical conductivity and large specific surface area [78]. The excellent electrochemical catalytic activity, the convenience of preparation and fabrication can make them a versatile material for the modification of electrodes [79]. Regarding the CAF, Sun et al. [80] presented an electrochemical sensor based on the electrocatalytic activity of Nafion/GR towards the oxidation of CAF on GCE. Owing to the unique properties of GR, including subtle electronic characteristics and strong adsorptive ability as well as the enhancement effect of Nafion, this sensor obviously promoted the sensitivity of the determination of CAF with the low detection limit. The cationic surfactant cetyltrimethylammonium bromide (CTAB)/GR modified GCE for the sensitive determination of CAF was also reported by Sun et al. [81]. In this case, the function of surfactant consisted in the improvement of the peak shape and sensitivity, and possessed antifouling capacity via inhibiting the

direct contact of substrate with the electrode surfaces [82]. The developed sensor exhibited the wide linear detection range, acceptable reproducibility, high sensitivity, long-term stability and low detection limit. Zhao et al. [83] demonstrated a new CAF voltammetric sensor based on combination of GO and Nafion on GCE which can be applied to the determination of CAF with excellent sensitivity and selectivity. The employment of Nafion had two functions: one intention is previously mentioned good affinity towards CAF and the other is the immobilization of GO on GCE [62]. Thus, modified GCE presented the good reliability and stability, had the superior immunity to some interference and offered the good possibility for extending the technique in routine analysis of CAF. GO combined with cerium hexacyanoferrate (CeHCF) modified GCE was applied for simultaneous determination of CAF and PAR in human urine with satisfactory results [84].

Carbon nanotubes (CNTs) are widely used in analytical chemistry due to their unique structure and extraordinary properties such as large surface area and efficient catalytic activity in charge transfer reaction when used as electrode material [85]. Yang et al. [86] developed the convenient and rapid method to fabricate GCE modified with multi-walled carbon nanotubes (MWCNTs) and Nafion for the sensitive determination of CAF. CNTs were homogeneously dispersed in Nafion solution thanks to the hydrophobic side chains and polar groups of Nafion. Compared to the bare GCE and Nafion/GCE, the Nafion/MWCNTs/GCE can remarkably increase the anodic peak current of CAF. The sensor surface was renewed by few repetitiously cycling in a blank solution. The study with similar conclusions using adsorptive stripping differential pulse voltammetry (AdSDPV) was performed by Zhang et al. [87]. Wei et al. [88] fabricated the GCE coated with the CNTs and nano-Pt for the determination of CAF. Because of high surface area, ultragentle and nanosized Pt particles had better catalytic activity compared with conventional particles. It enhanced the peak current of CAF and lowered oxidation overpotential also thanks to the unique properties of CNTs. The CNT paste electrode (PE) modified with Triton X 100 (TX 100) as in situ surfactant (ISS) was developed for very sensitive individual and simultaneous determination of CAF, PAR and ASP [89]. The results obtained demonstrated the synergistic effect of TX 100 and CNT/PE causative the enhancement of peak current of CAF. The improvement effect of CNT for CAF analysis was also confirmed by Habibi et al. [90] who presented the simple, fast, and reproducible procedure for the fabrication of a single-walled carbon nanotube modified carbon-ceramic electrode (SWCNT/CCE).

The most of above mentioned voltammetric methods cannot be used in *in vivo* analysis of CAF usually because of laboratory conditions. Recently, the simple and sensitive analytical methods are also needed in diagnostic systems due to the growing demand for lower detection limits or *in vivo* direct assays in the skin and in neuroscientific processes. For instance, the CAF and catechol were simultaneously analyzed with a bismuth-immobilized CNT/PE using SWV in electrolytic conditions [91]. This sensor was interfaced with an electrochemical instrument and the neuron of a fish brain or a rat brain to gain a neuronal current in real-time live direct assay. It is also applicable to organ monitoring, *in-vivo* diagnosis, and other methods that require physiological interface control. DNA immobilized onto a CNT/PE was examined with voltammetric assay for CAF [92]. The sensor could be implanted in a leaf skin or animal brain cell and used in real-time *in vivo* analysis of CAF.

Table 1. Summary of voltammetric methods for determination of CAF.

Electrode	Modifier	Technique	LCR (μM)	DL (μM)	Application	Year	Ref.
GPE	N/A	SWASV	93-2575	47.4	Tea	2004	[46]
EPPGE	N/A	SWV	0.02-100	0.008	Coffee, drugs, urine	2011	[47]
GCE	N/A	DPV	N/A	N/A	Coffee, tea	1979	[38]
GCE	N/A	DPV	0-256	NR	Drugs	1989	[39]
GCE	Nafion	DPV	0.995-10.6	0.798	Cola	2007	[33]
GCE	Nafion/GO	DPV	0.4-80	0.2	Cola, energy drink	2011	[83]
GCE	Nafion/GR	DPV	0.4-600	0.12	Cola, coffee	2011	[80]
GCE	Nafion/MWCNTs	DPV	0.6-400	0.23	Cola, tea	2010	[86]
GCE	Nafion/MWCNTs	AdSDPV	2.945-377.0	0.513	Cola, drugs	2011	[87]
GCE	Nafion/PST	LSV	0.3-100	0.1	Tea	2011	[75]
CME	Nafion/RuOP	SWV	5-200	2	Cola, tea, coffee	1998	[64]
CME	Nafion/RuOP	SWV	10-250	2.2	Drugs	1997	[65]
GCE	CTAB/GR	DPV	0.3-100	0.091	Soft-drink	2011	[81]
GCE	PAHNSA	SWV	0.06-40	0.137	Coffee	2012	[69]
GCE	PAP	DPV	0.05-10	0.001	Cola	2004	[70]
GCE	Cu^{II}TAPcSAM	DPV	5-1400	0.03	Cola, drugs, serum	2012	[71]
GCE	MIS/MWCNTs-VTMS	DPV	0.75-40	0.22	Coffee, energy drink	2012	[95]
GCE	MIPs/GNPs/MWCNTs	DPV	0.0005-0.16	0.00009	Tea	2012	[96]
GCE	Pt/CNTs	DPV	10-100	0.2	Cola, tea	2009	[88]
GCE	PT/TiO_2-GR	DPV	25-200	0.5	Human serum	2013	[72]
GCE	CeHCF/GO	DPV	1-130	0.52	Urine	2012	[84]
EA-GCE	N/A	DPV	0.1-100	0.02	Urine, drugs	2011	[40]
CPE	MIP	DPV	0.06-25	0.015	Tea	2010	[97]
CPE	BQ	SWV	500-8000	5.1	Coffee	2008	[76]
CPE	Bi-CNT	SWV	51.3-1026	0.182	Fish and rat brain	2008	[91]
CPE	DNA/CNT	SWV	0.512-61.7	0.35	Cell, skin	2009	[92]
CPE	ISS/CNT	AdSDPV	0.291-62.7	0.09	Urine, blood, drugs	2010	[89]
CPME	N/A	SWV	1-1000	0.348	Cola, tea, coffee	2012	[42]
CFUME	N/A	FSV	10-200	3.33	Drugs	2012	[43]
CCE	SWCNT	DPV	0.25-100	0.12	Cola, tea, coffee	2012	[90]
BDDE	N/A	LSV	1-400	NR	Cola, coffee	2002	[34]
BDDE	N/A	DPV	1-1000	0.16	Drugs	2012	[55]
BDDE	N/A	DPV	0.4-25	0.15	Cola, tea, coffee	2012	[56]
CP-BDDE	N/A	DPV	9.7-110	7	Drugs	2010	[57]
CP-BDDE	N/A	DPV	0.5-83	0.035	Drugs	2009	[58]
BDDE	Nafion	DPV	0.2-12	0.1	Cola	2010	[35]

Electrode: BDDE: boron-doped diamond electrode, CCE: carbon ceramic electrode, CFUME: carbon fiber ultramicroelectrode, CME: chemically modified electrode, CP-BDDE: cathodically pretreated boron-doped diamond electrode, CPE: carbon paste electrode, CPME: pseudo carbon paste microelectrode, EA-GCE: electrochemically activated glassy carbon electrode, EPPGE: edge plane pyrolytic graphite electrode, GCE:glassy carbon electrode, GPE: graphite pencil electrode, **Modifier:** BQ: 1,4-benzoquinone, CeHCF: cerium hexacyanoferrate, CTAB: cetyltrimethylammonium bromide, Cu^{II}TAPcSAM: self-assembled monolayer of non-peripheral amine substituted copper(II) phthalocyanine, GNP: gold nanoparticle, GO: graphene oxide, GR: graphene, ISS: in situ surfactant, MIP: molecular imprinted polymer, MIS: molecular imprinted siloxane, MWCNT: multi-walled carbon nanotube, PAHNSA: poly(4-amino-3-hydroxynaphthalene sulfonic acid), PAP: poly(4-aminopyridine), PST: poly(safranine T), PT: poly(taurine), RuOP: ruthenium oxide pyrochlore, SWCNT: single-walled carbon nanotube, VTMS: Vinyltrimethoxysilane, **Technique:** AdSDPV: adsorptive stripping differential pulse voltammetry, DPV: differential pulse voltammetry, FSV: fast scan voltammetry, LSV: linear sweep voltammetry, SWASV: square-wave anodic stripping voltammetry, SWV: square-wave voltammetry, **Other:** DL: detection limit, LCR: linear concentration range, N/A: not applicable, NR: not reported

Molecular imprinting techniques with predetermined recognition for target molecule has been proposed and developed rapidly in recent years [93]. Owing to the complementarity in shape and binding sites, the created nanocavities in synthesized molecularly imprinted polymers (MIPs) can exhibit high selectivity towards the imprinted molecules [94]. Thus, a sensor, combining the electrochemical method and molecularly imprinted technique, could be supposed to achieve the recognition and determination of CAF. The development of a novel sensitive molecularly imprinted electrochemical sensor for the analysis of CAF with excellent performance was described by Santos et al. [95]. The sensor was prepared onto the GCE modified with MWCNTs and vinyltrimethoxysilane (VTMS) recovered by molecularly imprinted siloxane (MIS) film prepared by sol-gel process and has the great potential in the real sample analysis. On the other hand, Kan et al. [96] used combination of MIPs with GNPs and MWNTs for the recognition and detection of CAF. The designed sensor showed the wide linear range and the extremely low detection limit of 90 pM. Moreover, the MIPs/GNPs/MWNTs/GCE possessed the specific recognition capability for CAF over other structures similar compounds as well as excellent stability and regeneration. The CAF-selective MIPs on CPE were synthesized by Alizadeh et al. [97]. The electrode was used for CAF measurement via a three-step procedure including extraction in the electrode, electrode washing and electrochemical measurement of CAF. Table 1 gives a summary of voltammetric methods for determination of CAF.

2.3. Potentiometric methods

Potentiometry is one of the simplest electrochemical techniques. The measurement enables the selective detection of ions in presence of various other substances [98]. In this context, the ion-selective electrodes (ISE) with liquid and polyvinylchloride (PVC) membranes have been developed for direct potentiometric determination of some alkaloids [99,100]. These monitoring systems have many advantages such as simplicity, selectivity, applicability to samples of different nature and possible interfacing with automated systems. Accordingly, Hassan et al. [101] introduced the first electrode for the determination of CAF based on the use of CAF-picrylsulfonate ion pair complex in 1-octanol as a liquid membrane. The electrode showed the fast response time, the high sensitivity, the reasonable selectivity, the long-term stability and wide working pH range (5.5-9). However, these results appeared to be misleading in the sequel, because the pK_a value of caffeinium ion was found to be around 0.7 [102] and the neutral form of CAF was predominant in the studied pH range. It is generally known that ISE should only respond to the ionic form and the results reported by Hassan et al. [101] showing a response to the neutral form of CAF, was questionable. Therefore on the basis of this fact, Katsu et al. [103] decided to reinvestigate the response characteristics of CAF electrode, taking into consideration the pK_a value, and constructed the new electrode with the combination of the cation-exchanger, tetrakis[3,5-bis(2-methoxyhexafluoro-2-propyl)phenyl]borate (HFPB), and the solvent mediator with high degree of dielectric constant, 2-fluoro-2-nitrodiphenyl ether (FNDPE).

The significant research and development activity has been devoted for the preparation of compact analytical devices for the determination of CAF including a bioactive sensing element integrated with a suitable transducing system. A biosensor based on inhibition of 3,5-cyclic

phosphodiesterase (CPDE) from bovine heart in combination with pH electrode for the detection of CAF in coffee was reported by Pizzariello et al. [104]. The potentiometric enzyme sensor was based on the hydrolysis of adenosine 3',5'-cyclic monophosphate (c-AMP) to adenosine 5'-monophosphate (AMP) and H_3O^+ ions through the effect of CPDE in the presence of the protein activator (calmodulin) and Ca^{2+}. When this enzymatic reaction was inhibited by CAF, the produced H_3O^+ were potentiometrically monitored and depended in an inversely proportional way to the concentration of CAF [105]. The sensor exhibited the advantages such as fast response, short conditioning time and low cost of the instrumentation as well as excellent correlation between observed and predicted CAF values was observed.

The potentiometric membrane sensor for the determination of CAF in coffee, drugs and urine based on 4-tert-butyl-2,6-diphenyl-2H-thiopyran (BDT) was presented by Siavash et al. [106]. The best performance was achieved with a membrane composition, consisting of 32% PVC, 56% *ortho*-nitrophenyloctyl ether (*o*-NPOE), 4% BDT and 8% oleic acid (OA) with results displaying the good agreement with the standard procedures.

Table 2. Overview of potentiometric applications for determination of CAF.

Type of electrode	Response time (s)	Composition of electrode	LCR (µM)	DL (µM)	Application	Year	Ref.
Liquid membrane	20-90	PS, 1-octanol	1-10000	1	Drugs	1985	[101]
Liquid membrane	10	HFPB, FNDPE	0.01-10000	50	Drugs	2008	[103]
pH glass electrode	120-240	CPDE-CM	0-20600	3.1	Coffee	1999	[104]
PVC membrane	N/R	o-NPOE, BDT, OA	0.3-10000	0.2	Coffee, drugs, urine	2009	[106]
Ag wire	15	MAA, EGDMA, AIBN	0.01-10	0.005	Syrup	2012	[108]
Sb	N/A	N/A	N/R	N/R	Pepsi, tea, drug	1993	[109]

AIBN: α,α′-azoisobutyronitrile, BDT: 4-tert-butyl-2,6-diphenyl-2H-thiopyran, CPDE-CM: 3',5'-cyclic phosphodiesterase with calmodulin, DOP: di-n-octylphthalate, EGDMA: ethylene glycol dimethacrylate, FNDPE: 2-fluoro-2-nitrodiphenyl ether, HFPB: tetrakis[3,5-bis(2-methoxyhexafluoro-2-propyl)phenyl]borate, MAA: methacrylic acid, OA: oleic acid, o-NPOE: ortho-nitrophenyloctyl ether, PS: picrylsulfonate, PVC: polyvinylchloride, N/A: not applicable, N/R: not reported, LCR: linear concentration range, DL: detection limit

Concerning the MIPs based potentiometric sensors, they are rarely reported due to the low sensitivity [107]. However, in the study of Guo et al. [108], the MIP-modified coated-wire electrode for the monitoring of CAF was developed. This strategy was founded on the preparation of CAF template getting H_3O^+ ions from water which can be measured potentiometrically by the polymeric membrane of ISE. The application of direct current differential electrolytic potentiometry (dc DEP) to the titration of CAF in acetic anhydride-toluene mixture was investigated by Abdennabi and Sultan [109]. The very stable low current source was employed to polarize the antimony electrodes which were examined as an indicating system. A list of potentiometric methods with basic characteristics for the determination of CAF is given in Table 2**.**

2.4. Amperometric methods

Modern analytical methods applicable to routine and research laboratories require some characteristics such as easy automation, high throughput analysis, sensitivity, selectivity, accuracy and precision. Flow injection analysis (FIA) associated with amperometric detection (AD) fulfills these desirable characteristics and therefore has been extensively applied for the development of analytical methods. The possibility of using a potential pulse for cleaning step is also crucial if analyte with adsorptive characteristics such as CAF is analyzed. The automatic procedure based on FIA was developed for the determination of CAF in soft drinks using the AD (+1.7 V *vs*. Ag/AgCl electrode) [110]. This system was very simple, easy to operate, inexpensive and rather economical considering the handling and use of the reagents. The short time of contact of CAF with working GCE diminished the adsorption effects, which allowed the use of this electrode over the working day after being submitted to the single mechanical polishing without any electrochemical treatment. Similarly, the use of multiple pulse amperometric detection (MPAD) can prevent the contamination of the working electrode surface due to the application of cleaning potential pulse. Silva et al. [111] reported for the first time a simple strategy (use of the correction factor) for simultaneous analysis of PAR and CAF using FIA-MPAD with single working BDDE. The determination was possible using a home-made electrochemical wall-jet cell coupled to a single-line flow system.

An alternative to the FIA technique is the batch injection analysis (BIA) introduced by Wang and Taha [112]. The BIA technique provides the additional advantages such as the elimination of typical drawbacks associated with pump and valves of the FIA system, disposal of reagent/carrier solutions and possibility of developing portable BIA instruments. This system was also suggested for the determination of CAF with dual pulse amperometric detection (DPAD) on BDDE [113].

Sarath Babu et al. [114] developed the amperometric microbial biosensor (MIC-B) for the analysis of CAF in beverages using immobilized whole cells of *Pseudomonas alcaligenes* (PA) capable of degradation of CAF. Interestingly, this biosensor was highly specific for CAF and the response to interfering compounds such as THO, theobromine and sugars was found to be negligible. Akyilmaz and Turemis [115] devised the biosensor based on the alkaline phosphatase enzyme (ALPE) immobilized on gold screen printed electrode (GSPE). The CAF competitively inhibited ALPE and thus determination was based on this inhibition effect. The principle of the measurement was founded on the evaluation of the differentiation of biosensor responses in the enzymatic reaction catalyzed by ALPE in the absence and the presence of CAF. The effort of Vinjamuri in his master thesis [116] was focused on the selectivity study of detection of CAF and theobromine on molecularly imprinted polypyrrole (MPPY) electrode surface. He used and compared the techniques such as pulse amperometric detection (PAD) and electrochemical impedance spectroscopy (EIS) with results showing no statistical difference. Table 3 shows the overview of amperometric sensors for the determination of CAF.

Table 3. Amperometric sensors for determination of CAF.

Electrode	Technique	Number of injection per hour	LCR (µM)	DL (µM)	Application	Year	Ref.
GCE	FIA-AD	120	10-80	0.21	Soft drinks	1998	[110]
BDDE	FIA-MPAD	140	5.1-1620	0.87	Drugs	2011	[111]
BDDE	BIA-DPAD	> 60	1.8-20	0.72	Drugs	2011	[113]
PA-MIC-B	AD	N/A	510-5130	N/R	Coffee, tea, cola	2007	[114]
GSPE-ALPE-B	AD	N/A	1-10	0.08	Coffee, tea, cola	2010	[115]
MPPY/Pt	PAD, EIS	N/A	1000-20000	N/R	Coffee, tea	2008	[116]

Electrode: ALPE-B: alkaline phosphatase enzyme biosensor, BDDE: boron-doped diamond electrode, GCE: glassy carbon electrode, GSPE: gold screen printed electrode, MPPY: molecularly imprinted polypyrrole, PA-MIC-B: Pseudomonas alcaligenes microbial biosensor, **Technique:** AD: amperometric detection, BIA: batch injection analysis, DPAD: dual pulse amperometric detection, EIS: electrochemical impedance spectroscopy, FIA: flow injection analysis, MPAD: multiple pulse amperometric detection, PAD: pulse amperometric detection, **Others:** DL: detection limit, LCR: linear concentration range, N/A: not applicable, N/R: not reported

2.5. Molecular polymer piezoeletric sensors

As it was mentioned in previous sections, MIPs are represented as the valuable recognition element in (electro)chemical sensors. The application of MIPs on a piezoelectric quartz crystal (PQC) sensors is an especially potentially attractive area although their slow development could indicate the problems in integration of MIP reagent with PQC transducers [117]. Moreover, the next problem comes from the interference produced by other compounds (usually xanthine derivatives), commonly present in the coffee and tea samples, having the similar structure to CAF.

The promising biomimetic sensors for the measurement of CAF were explored by Ebarvia et al. [118,119]. The sensors were developed through the incorporation of the MIP film on the electrode surface of PQC and provided very good linearity, high sensitivity, and high selectivity. The achieved detection limits of 0.2 and 0.3 pM belong to the lowest ones from overall electrochemical methods dealing with the determination of CAF. The MIPs in these works were prepared by co-polymerization of methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA) in the presence of azobis(isobutyronitrile) (AIBN) as initiator, CAF as template molecule and chloroform as solvent. On the other hand, Zougagh et al. [120] used the similar conditions for the construction of on-line supported liquid membrane PQC system for the determination of CAF in coffee and tea samples. This study described the first use of SLM coupled on-line with PQC detector coated by MIP. The proposed assembly provided all the advantages of an on-line system as regards automation, in addition to good selectivity, acceptable sensitivity and precision. The method had the enhanced selectivity by avoiding the interfering matrix constituents, such as xanthine, THO, nicotinic acid and chlorogenic acid.

The liquid phase biomimic bulk acoustic wave (BAW) sensor fabricated by coating of the MIP for the determination of CAF in human urine and serum was introduced by Liang et al. [121]. The selectivity of the sensor was checked by testing the structural analog THO and less interference was observed. When the sensor was modified with PVC immobilized MIP particles, it showed the high selectivity to CAF. It was shown that BAW sensor was not only sensitive to the mass change on the

sensor surface, but also to the physico-chemical properties of the surrounding medium. The viscosity and the density of the sample had the explicit influence on the response of the sensor.

The selective binding of CAF to polymers is of great interest in developing CAF-PQC sensors also in next papers focused on the study of binding interactions CAF-polymer [122] and the use of phase inversion precipitation method for preparation of polyacrilonitrile (PAN) copolymers, respectively [123]. It was found that the interactions can be significantly affected by the solvent polarity and the nature of the functional monomers and also demonstrated how the selectivity for CAF by some polymers can be affected by both hydrophobic and structural-type interactions. The survey of PQC sensors coated by MIPs is listed in Table 4.

Table 4. Overview of piezoeletric quartz crystal (PQC) sensors coated by MIPs for detection and determination of CAF.

Monomers/cross-linker	Initiator	Response range (nM)	DL (nM)	Application	Year	Ref.
MAA/EGDMA	AIBN	0.005-5130	0.0002	N/R	2004	[118]
MAA/EGDMA	AIBN	0.005-513000	0.0003	N/R	2005	[119]
MAA/EGDMA	AIBN	5-100000	5	Urine, serum	1999	[120]
MAA/EGDMA	AIBN	50-5100	28	Coffee, tea	2005	[121]
MAA/DVB	AIBN	N/A	N/A	N/A	2001	[122]

AIBN: α,α´-azoisobutyronitrile, DVB: divinylbenzene, EGDMA: ethylene glycol dimethacrylate, MAA: methacrylic acid, N/A: not applicable, N/R: not reported, DL: detection limit

3. CONCLUSIONS

Electrochemical approaches for determination of CAF have been reviewed herein. From this collection it can be seen that analytical studies in this field register a sharp increase in recent years. Four comprehensive tables present the reported available data within the text and summarize the results especially with respect to the used working electrode material, linear concentration range and detection limit. It was noted that determination of CAF has predominantly been performed by voltammetric methods using carbon-based electrodes (GCE, CPE), with emerging research moving towards the greater variety of modified electrodes with the lowest detection limit of 90 pM. The new applications of BDDE are promising contribution thanks to the low adsorption ability and the widest usable potential range capable of comfortable oxidation of CAF at high positive potential. Sensitive potentiometric methods based on liquid and PVC membranes have been used, with fast response times and wide linear concentration ranges in the level of 3-6 orders. Occasionally, some amperometric methods have been employed in analysis of CAF with emphasis on the utilization of injection analysis and biosensors. The use of PQC sensors coated by MIPs with very low detection limits and wide linear concentration ranges in the detection and determination of CAF is also discussed. Building on these facts, further advancement in this field can proceed in order to develop the automatic electrochemical sensor for fast, simple, sensitive and selective determination of CAF.

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