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Review Paper

Electro-oxidation and determination of atenolol – A review

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Abstract

This mini review is dedicated to electrochemical studies on atenolol. Electrochemical methods are known for its low cost, fast response, simple and selective alternates to classical methods such as chromatographic and spectral methods. However till date, a review on electro oxidation and determination of atenolol has not been reported. Major part of this article deals with voltrammetric sensors developed using untailored and tailored electrodes of carbon for the detection of atenolol. In this mini review, amperometric, potentiometric and capillary electrophoresis methods were also discussed. The methods developed are used successfully for the detection of atenolol in different samples like urine, serum, natural water and tablet dosages.

Keywords: Atenolol, voltammetry, nanoparticles, modified electrodes, sensor.

Introduction

One of the growing diseases of medical concern is hypertension. There is remarkable increase in the use of β-blockers which fall in the category of antihypertensive medications which are used towards the hypertension cases in last few decades. Among them, Atenolol (ATN) (-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide) (Figure-1) is a beta blocker prescription used to treat chest pain relate with heart and elevated blood pressure. It is also used for anti-angina treatment to relieve symptoms, improve tolerance and as an anti-arrhythmic to help regulate heartbeat and infections. It is also used in management of alcohol withdrawal, in anxiety states, migraine prophylaxis, hyperthyroidism and tremors[1]. It is taken by mouth or by injection into a vein. It can also be used with other blood pressure medications. The derivative of oxidation product of atenolol is being used in plant growth hormones, herbicides, etc. β -Blockers are extremely poisonous and have very slight haling range. Some of the adverse effects of overdose of atenolol are lethargy, disorder of respiratory drive, wheezing, sinus pause, bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycemia[2,3].

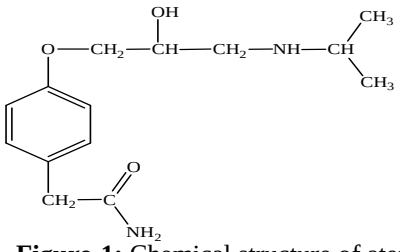

Figure-1: Chemical structure of atenolol.

Interestingly, ATN among all the β-Blockers was determined and reported by different analytical methods more than other β-Blocker drug molecules. The literature review showed that numerous chromatographic methods have been developed for the determination of ATN such as high-performance liquid chromatography-diode array detector[4], Flow injection chemilunescence using cadmium sulfide quantum dots[5], enantioseparation and determination by liquid chromatography[6], spectrophotometric method[7], high performance liquid chromatography[8], liquid chromatography–high resolution mass spectrometry[9], excitation–emission fluorescence matrices[10].

These methods are having excellent sensitivity, selectivity and detection limit for determination of ATN. The majority of the reported techniques need separation, and some methods require pretreatment before analysis. These methods also require well trained personnel so that applications of these methods in routine practice are limited. These methods reported are time consuming, concentrated on solvent-usage and requires costly devices and maintenance. Electrochemical analysis of analyte is green method in analytical chemistry[11,12]. Now a days, much research is going on focusing the development of electrochemical sensing devices to monitor environment, for assaying clinical trials or for process control. Electrochemical sensors satisfy many of the requisites for such tasks particularly owing to their specificity, rapid response, sensitivity and simplicity of preparation.

The electrochemical methods for the quantification of ATN on different electrode materials (on modified and unmodified electrodes) are reviewed and summarized in this article. To the best of our knowledge, there are no official attempts on summary of electrochemical methods of detection of ATN are published till date in literature. Thus, a summary of potentiometric, voltammetric and amperometric sensors for the detection of ATN is provided in following sections and the vital

uniqueness of voltammetric determinations were listed in Table-1.

Electrochemical methods

Voltammetry at bare carbon electrodes: One of the extensively used material which is based on carbon in the electrochemical laboratory is glassy carbon electrode (GCE). As compared to other working electrodes, the GCE has elevated over potential for evolution of oxygen and low over potential for hydrogen evolution which increases its working potential window. Also the GCE shows higher affinity toward analyte which produces the high and resolute current peaks which make electrochemical analysis both the qualitative and quantitative easy as compared to other electrodes. It has significant properties like high temperature resistance, extreme resistance to chemical attack, and impermeability to gases and liquids. Because of all these properties, GCE is widely used as an electrode material in electrochemical equipments. Some electrical properties of GCE such as impedance, pH sensitivity and polarization characteristics have been studied[13].

The first report on electrochemical behaviuor of ATN was reported by us on bare GCE in 2008[14]. This study showed that ATN undergoes electro oxidation (Figure-2) at GCE and can be determined. This report was against the claim made in 2006[15] that there was no peak observed on GCE by ATN. This work was revisited in 2008[16] and said that GCE modified with C_{60} was blocking the surface of the electrode and oxidation peak was visible on bare GCE. In our work, ATN gave an oxidation peak at 1.097 V in methanol medium with 0.1M TMAC as supporting electrolyte as shown in Figure-2. The effect of scan rate, concentration, temperature, solvent and dielectric constant were discussed. The peak current was linear from 2.0-10.0 mM of ATN.

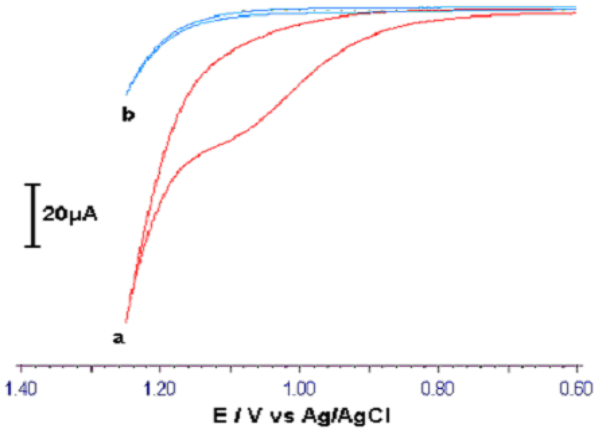

Figure-2: Obtained cyclic voltammogram in 0.1M TMAC on GCE for 2mM atenolol: (a) atenolol, (b) blank at 50mVs^{-1}scan rate.

Among carbon based electrodes, carbon paste electrodes (CPEs), due to exceptional property such as easy chemical modification, ease of renewability of the electrode surface, and very much compatible with a range of electron mediators, have been used widely in voltammetric studies[17]. The second report on bare carbon electrode on CPE was also reported by us in 2009[18]. Wherein we used CPE in phosphate buffer at pH 10.4, ATN showed oxidation peak at about 0.9 V. this peak potential value is lesser than that observed at bare GCE. It was very interesting to note that, ATN has undergoing oxidation only in alkaline conditions and with rise in pH, the peak potential linearly shifts to less positive values. Differential pulse voltammetry (DPV) was used to analyse ATN. The calibration curves were obtained for ATN in the range of 100 to 20µM with limit of detection (LOD) of 0.587µM. This scheme has been productively used for the determination of ATN in the pharmaceutical sample.

Voltammetry at modified electrodes

From the past few years, for the voltammetric measurements, various types of customized electrodes were constructed and used in different ways. This is to boost the sensitivity, selectivity and constancy of the measurements, the electrodes customized with different molecules / materials have been developed for determination of ATN electrochemically. Nevertheless the bulk of the modified electrodes have successfully detected the concentrations of ATN, still the challenging tasks for the researchers are the fabrication of the electrochemical sensor. In 2006, Goyal et al made first attempt to determine ATN on gold nanoparticles modified indium tin oxide electrode[19]. They used DPV to determine ATN in drug formulations and urine at ph of 7.2 in 1.0M phosphate buffer solutions without any preliminary treatment. The linear calibration curve was obtained in the range 0.5µM to 1.0mM with LOD of 0.13µM. The screen printed electrodes have the characteristics like fast response, reliable, versatile and are inexpensive. Recently, an MgO nanoplatelets modified screen printed electrode was used to determine ATN along with nifedipine. They carried out the determination in Britton-Robinson buffer at pH 9.0 using DPV. The MgO nanoplatelets were found to show improved voltammetric response because of electrocatalytic effect as compared to bare screen printed electrodes[20]. At a pH of 9.0, linear responses were from 6.66 to 909.09 µM with LOD of 1.76µM. Another report using screen printed electrode modified with calixarene was reported by Gabriele et al in 2010[21]. They synthesized and used six different calixarenes and studied electrochemical behaviuor of three β-blockers including ATN. Pankaj and Goyal reported the determination of ATN at amino functionalized Graphene oxide and polymer composite electrode[22]. They used a conducting polymer, poly 4-amino-3-hydroxy-1-naphthalenesulfonic acid with amino functionalized graphene oxide and the calibration curve was obtained in the range 0.1 to 300µM with LOD of 20 nM. This analytical method showed 97% recovery rates and was used for ATN detection in tablet dosage forms and biological fluids.

Priscila reported a polymer composite graphite electrode using DPV[23]. Their determination of ATN was very sensitive and

surface renewing was not needed between successive runs. Boron doped diamond is an outstanding electrode material which has greater material characteristics. Electrochemical reactions which are occurring in the wide potential window can be investigated since boron doped diamond has largest electrochemical potential window as compared to electrodes such as glassy carbon, gold and platinum. There are three reports for determination of ATN using boron doped diamond electrode. The first one was reported in 2010[24]. They used square wave voltammetry to analyse ATN at very low pH of 1.0. At this strongly acidic medium LOD was 0.93µM with recoveries ranging from 92.5% to 106.0%. Cathodically pretreated boron doped diamond electrode was described in 2016[25]. Square wave voltammetric method was used and LOD was 0.22µM and was used to determine ATN in pharmaceutical formulations. Recently Jessica and Elen reported detection of ATN using anodically pretreated boron doped diamond electrodes using TRIS buffer at pH 8.0[26]. DPV was used to quantify ATN and LOD was 0.999µM and the method was used to analyse ATN in commercially available dosages.

Innocenzo et al determined ATN along with other β-blockers, propranolol and nadolol using polycrystalline gold electrode[27]. They carried out DPV measurements in phosphate buffer solution of pH 2.5 along with about 22% of acetonitrile and achieved a LOD of 20µM. A novel ATN sensor was developed by Ebrahim and co[28]. ATN got electro oxidized at 2-acrylamido-2-methyl-1-propanesulfonic acid sodium salt (AMPSNa) doped PPy electrode in 1.0 M phosphate buffer solution. An oxidation peak was observed at 0.789 V indicating that; modified electrode has electrocatalytic activity towards oxidation of ATN. The DPV was used to determine ATN with LOD of 1.0 nM. Very recently a novel cobalt ferrite/graphene magnetic nanocomposite ($CoFe_2O_4$/GMNC) electrode was developed for the study of voltammetric behavior of ATN[29]. This nanocomposite electrode had showed electrocatalytic action for oxidation of ATN and can be used as a sensor of ATN. In 2012, another composite electrode was used to determine ATN in environmental water samples and pharmaceutical formulations[30]. By DPV procedure observed LOD was 2.23 µM and it showed excellent recovery values for determination of ATN in water samples.

Voltammetry at modified carbon electrodes

The carbon based electrodes; GCE and CPE can be easily modified using miscellaneous modifiers. Thus modified electrodes show excellent electro catalytic activity towards redox behavior of any drug molecule. The first report on modified CPE came in 2010 by Behpour and team[31]. They studied the nanogold-modified CPE that showed significant improvement in peak current and shift in peak potential. Using DPV in a Britton-Robinson buffer solution of pH 10, they obtained LOD of 730nM and successfully applied this method to determine ATN in tablets and human urine. In the same year, same authors reported a sensor for the determination of ATN along with acetaminophen on a gold nanoparticle modified CPE[32]. It was a simple and rapid determination in Britton-Robinson buffer with LOD of 0.073µM and this method was used to determine ATN in tablet dosage formsand human plasma. A ferrocenyl schiff base modified electrode was developed by Masumeh and co[33]. They used N-4,4'-azodianiline (ferrocenyl Schiff base) complex and multi wall carbon nanotubes to chemically modify CPE. It was a very sensitive sensor for ATN with oxidation peak appearing at 0.55 V due to electrocatalytic nature of modifiers. The DPV was used to quantify ATN with LOD of 0.08µM at pH 6.0. In 2014, CPE modified with Fe_2O_3, a magnetic nanoparticle grafted with 3-aminopropyl group, was developed[34]. The anodic peak current enhanced due to adsorption of ATN onto the electrode. ATN was determined simultaneously in this work long with amiodarone by DPV in Britton-Robinson buffer solution at pH 4.0. The behavior of ATN at CPE modified with mordenite zeolite was described[35]. They reported that, at bare CPE atenolol has not shown any peak, which is in contrast to our report[18]. Nevertheless, the modifier zeolite improves the sensitivity owing to its electrocatalytic nature. With LOD of 0.1 µM using DPV in acetate buffer solution of pH 5.0 was reported.

The copper oxide nanoparticle is a promising one with many applications including its use as a electrocatalyst for redox reactions[36]. A copper oxide nanoparticle modified CPE was developed to study electrochemical behavior of ATN along with another two β-blocker drug molecules carvedilol and propranolol[37]. The increase in anodic peak current indicates that copper oxide nanoparticles are promoting the oxidation at the modified electrode. In a buffer solution, the LOD of 12.0 µM was reported in this work.

Over the years, the unique properties of carbon nanotubes (CNTs) make them attractive for application as chemical sensors, in general and particularly in voltammetric detection. CNTs were discovered using transmission electron microscopy by Iijima in 1991[38], CNTs have been used and found applications in several investigations in chemical, physical and material areas due to their excellent structural, mechanical, electronic and chemical properties[39]. The CNTs have the capability to catalyze charge transfer reactions because of their clever electronic properties when used as an electrode[40]. The customization of electrode and the substrates with multi-walled carbon nanotubes (MWCNTs) for application in analytical sensing has been showed to result in low detection limits, high sensitivities, reduction of over potentials and resistance to surface fouling. MWCNTs have been introduced as electro-catalysts and CNTs modified electrodes have been documented to give excellent performance in the study of a number of biological species[41]. Because of all these properties, CNTs have become very attractive modifiers. There was a report for the determination of ATN along with betaxolol using MWCNTs modified CPE[42]. They used multivariate curve resolution-alternating least squares assisted by DPV in a Britton-Robinson buffer solution to detect both molecules. This proposed method

was applied to determine ATN in human plasma and LOD of the method was 0.29µM. Recently a newly synthesized ceramic material viz, $DyMnO_3$-ZnO ceramic green nanocomposite was used to modify CPE[43]. This nanocomposite demonstrated superior electrocatalytic activity for the oxidation of ATN and can be used as a sensor for drug molecules. However they have not quantified ATN in this report.

The first report on behaviuor of ATN at modified GCE was described by us in 2011[44]. Wherein, we used MWCNTs to modify GCE. The oxidation peak for ATN was broad and weak at the bare GCE since the electron transfer was slow (Figure-3), however, the peak was more stronger at the at the MWCNT-modified GCE. The oxidation peak was at about 0.94 V when MWCNT-modified GCE was used against the peak at about 1.06 V when bare GCE was used (Figure-3), with significant improvement in the peak current because of MWCNTs showing electro-catalytic effect. After the successive scan, the peak current decreased greatly and finally remained unchanged (Figure-4). This phenomenon may be attributed to the adsorption of oxidative product of ATN at the modified electrode surface. Influence of parameters like amount of MWCNTs, accumulation potential and time, pH and scan rates were studied. The oxidation peak of ATN can be assigned to the oxidation of secondary amine group, as documented in the literature[45]. The number of electrons transferred in the process was 2 and the pH dependent behavior of oxidation peak potential showed that, the number of electrons and protons involved in the process is equal. ATN looses an electron to form cation radical, which on losing a proton and an electron in subsequent steps to form a quaternary Schiff base. Thus resulted quaternary Schiff base was rapidly hydrolyzed to an aldehyde, 2-[4-(2-Hydroxy-3-oxo-propoxy)-phenyl]-acetamide and to a primary amine, isopropylamine as shown in Figure-5. The DPV was used to quantify the amount of ATN (Figure-6). In phosphate buffer solution of pH 8.0, linear calibration curve obtained in the range of 6.0 to 20.0µM with LOD of 23.4nM.

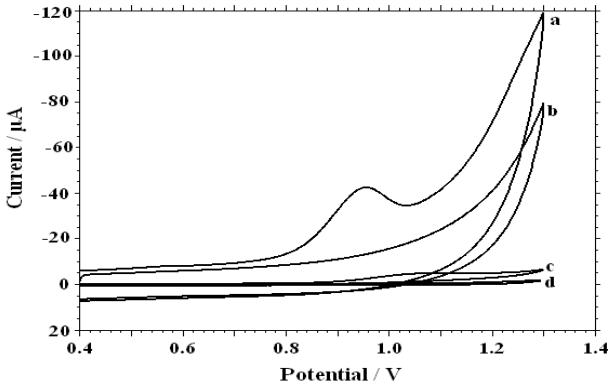

Figure-3: Recorded cyclic voltammograms for 0.10 mM ATN on MWCNT-modified GCE (a) and bare GCE (c) and blank voltammograms of MWCNT-modified GCE (b) and bare GCE (d). Scan rate: 50mVs^{-1}; supporting electrolyte: 0.2M phosphate buffer with pH 8.0; accumulation time: 60s (at open circuit); volume of MWCNTs suspension: 12µl.

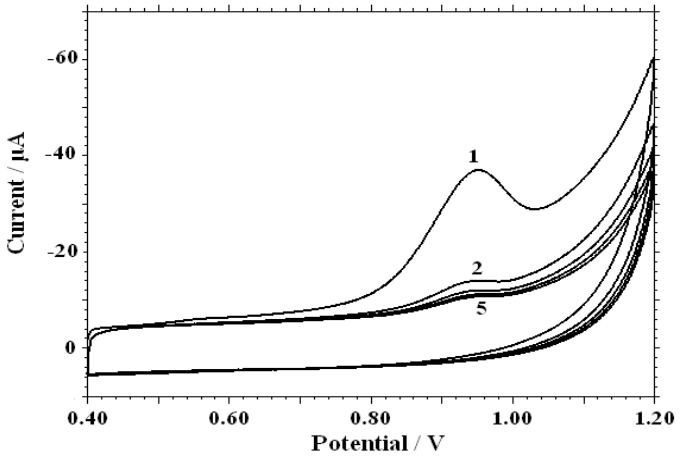

Figure-4: On the MWCNT-modified GCE, cyclic voltammograms recorded successively for 0.10mM ATN. Other conditions are as in Figure-3.

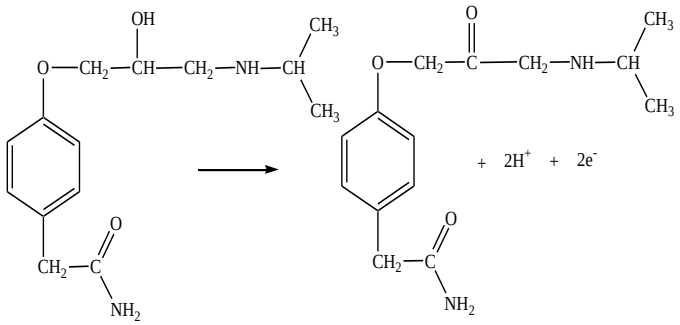

Figure-5: Probable mechanism for the oxidation of ATN.

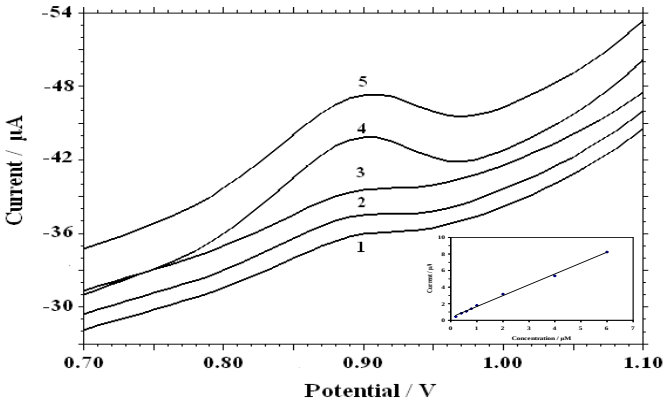

Figure-6: Differential-pulse voltammograms of MWCNT-modified GCE in ATN solution at different concentrations: 0.2 (1), 0.4 (2), 0.6 (3), 2.0 (4), and 4.0 (5) µM. Inset: Plot of the peak current against the concentration of ATN.

Nanoparticles were used extensively as a modifier to develop the electrochemical sensors. A platinum nanoparticle-doped multiwalled carbon-nanotube-modified glassy carbon electrode has been reported for the determination of ATN along with another β-blocker drug propranolol[46]. Phosphate buffer solution of pH 7.4 was used to determine both the β-blockers selectively

with LOD of 1.17μM for ATN. Gold nanoparticles find their application in medicine and industry. These can be used as modifiers because of their properties like high electrical conductivity, high surface area and easily compatible nature. A gold nanopartile MWCNTs modified GCE was developed to quantify ATN and Losartan Potassium simultaneously[47]. They carried out square wave voltammetry in Britton-Robinson Buffer at pH 10.0 with LOD of 0.09μM.

Another easy way of modifying the carbon based electrodes is to polymerize the modifier on to the surface of the electrode by simple electro deposition method. These poly modified electrodes are very sensitive and selective in nature. One of those kinds of work was described by Stela in 2011 for the determination of ATN at multicomponent nanostructered assembly of amino acid[48]. They covered GCE with layers of poly (glutamic) acid/cysteine followed by covalent attachment of gold nanoparticles which are citrate capped. Linear sweep voltammetry showed oxidation peak at about 0.65 V with LOD of 0.39μM. A poly-dopamine modified GCE has been developed[49]. They prepared modified electrode by electro deposition of dopamine, which showed good sensitivity and selectivity with a LOD of 27nM. These voltammetric methods of determinations were summarized in Table-1.

Table-1: Outline for the detection of ATN by voltammetric method

Type of Electrode	Modifier used	Technique	LOD (μM)	Reported Year	Reference
GCE	N/A	CV	200.0	2008	14
CPE	N/A	DPV	0.587	2009	18
ITOE	AuNPs	DPV	0.130	2006	19
SPE	MgONPLs	DPV	1.760	2017	20
GCE	AFGO/PCE	DPV	0.002	2016	22
BDDE	N/A	SWV	0.930	2010	24
CP-BDDE	N/A	SWV	0.220	2016	25
AP-BDDE	N/A	DPV	0.999	2018	26
PGE	N /A	DPV	20.00	2016	27
AMPSNa-PPy	N/A	DPV	0.001	2011	28
G-ECE	N/A	DPV	2.230	2012	30
CPE	NAu	DPV	0.073	2010	31
CPE	AuNPs	DPV	0.073	2010	32
CPE	FSBC/MWCNTs	DPV	0.080	2015	33
CPE	NFO	---	----	2014	34
CPE	MZ	DPV	0.100	2010	35
CPE	CON	DPV	12.00	2011	37
CPE	MWCNTs	DPV	0.290	2013	42
GCE	MWCNTs	DPV	23.40	2011	44
GCE	PNP/ MWCNTs	DPV	1.170	2015	46
GCE	AuNPs/ MWCNTs	SWV	0.090	2018	47
GCE	PGA/CY/AuNPs	LSV	0.390	2011	48
GCE	PD	DPV	0.027	2015	49

Electrode: GCE: glassy carbon electrode, CPE: carbon paste electrode, ITOE: indium tin oxide electrode, SPE: screen printed electrode, BDDE: boron doped diamond electrode, CP-BDDE: cathodically pretreated boron doped diamond electrode, AP-BDDE: anodically pretreated boron doped diamond electrode, PGE: polycrystalline gold electrode, AMPSNa-PPy: 2-acrylamido-2-methyl-1-propanesulfonic acid sodium salt-polypyrrole, G-ECE: graphite epoxy composite electrode. **Modifier:** NAu: nano gold, AuNPs: gold nanoparticles, FSBC: ferrocenyl Schiff base complex, MWCNTs: multi-walled carbon nanotubes, NFO: nano ferric oxide, MZ: mordenite zeolite, CON: copper oxide nanoparticle, PNP: platinum nanoparticle, PGA: poly (glutamic) acid, CY:cysteine, PD: poly-dopamine. Technique: CV: cyclic voltammetry, DPV: differential pulse voltammetry, SWV: square wave voltammetry, LSV: linear sweep voltammetry. **Other:** LOD: limit of detection.

Amperometric methods of analysis

The modern methods of analysis valid to regular and research laboratories require some properties like easy automation, exceptional sensitivity, high throughput analysis, good selectivity, accuracy and precision. One of the analytical method which fulfills these criteria is Flow injection analysis (FIA) associated with amperometric detection. Therefore this method has been used widely for the development of analytical methods. If the analyte is having adsorptive properties like ATN has, then there is a possibility that one can use potential pulse for leaning step. The automatic procedure based on FIA was developed for the determination of ATN in pharmaceutical formulations using a CPE[50]. This method was very simple, low cost, highly sensitive, very fast, reliable and most importantly environmentally friendly. In this method, the linear range was from 50 to 1000µM, with a LOD of 8µM. Another work on amperometric detection by FIA was done using a bare graphite-polyurethane composite electrode[51]. The said method has a linear calibration curve in the range 0.2 to 3.0mM with LOD of 18.1µM.

Batch injection analysis is an alternate to FIA. A bath injection analysis with pulsed amperometric detection using boron doped diamond electrode for sequential determination of ATN together with amlodipine was reported[52]. Present method was robust, simple, precise, less volume of waste with LOD for ATN 0.073 µM. In the year 1995 only, a high performance liquid chromatography with amperometric detection was reported for the determination of six β-blockers including ATN[53]. At a pH of 6.5, amperometric detector was equipped with GCE. This method was used to quantify all β-blockers with good recovery rates. Reneta and team developed an amperometric method to determine ATN in pharmaceutical formulations and urine by Layer by Layer technique on a $BiVO_4$–Bi_2O_3/ITO electrode in 2016[54]. Using this composite electrode in $NaNO_3$ as supporting electrolyte, linear calibration curve was obtained for ATN in the range 50.0–800.0µM with LOD of 0.459µM. $BiVO_4$–Bi_2O_3 electrode showed good selectivity and repeatability, simplicity, cost effective and is stable without the need for renewing the surface before each measurement. A novel method was developed by Lei and co-workers using carbon nanofibre paste electrode using capillary electrophoresis coupled with amperometry for the determination of three β-blockers simultaneously[55]. The carbon nanofibre paste electrode showed excellent electrocatalytic activity and in a phosphate buffer of pH 8.5, ATN has LOD of 0.01µM. This method has the features like low cost, good performance and easy preparation method of electrode.

Capillary electrophoresis and Potentiometric methods

The capillary electrophoresis (CE) technique was well established analytical tool and in last 30 years it has been developed very well. This CE is characterized as a dominant separation technique because it is showing high efficiency, less analysis time and low analyte and reagent consumption. There was method develop to determine ATN along with its analogy Metoprolol using CE coupled with a tris (2,2′-bipyridyl) ruthenium (II) by electrochemiluminescence detection technique[56]. The LOD was reported to be 0.075µM for ATN and above method was applied to analyse ATN in spiked urine samples satisfactorily. Another method was described for the determination of three β-blockers by CE with electrochemiluminescence using Poly-β-cyclodextrin as an additive[57]. The additive added improved the separation of three analytes with a LOD of 0.5µM for ATN. The β-cyclodextrin was having a cavity that can be used to accommodate drug molecules so that better separation can be achieved.

Potentiometric determination of an analyte was also a way to develop electrochemical sensors. For the determination of ATN, an ion selective electrode was developed[58]. The ion selective electrode consists of PVC membrane with atenolol-tetrakis (p-chlorophenyl) borate ion-pair complex. This ion selective electrode showed LOD of 10 µM and can be used to detect ATN in tablets, urine and serum samples. A polymeric membrane electrode of ATN and phosphomolybdic acid association complex was constructed to determine ATN potentiometrically[59]. The method was stable, reproducible and fast with LOD of 1 µM.

Conclusion

This review outlines some of the current electro oxidation and detection of ATN in tablet dosages, urine and serum samples, because ATN is being used widely to control hypertension and also as a doping agent. The electrochemical sensors used were based on bare or modified carbon based electrodes; either CPE or GCE, modified usually with nano dimension materials, which are showing electrocatalytic effects. Few amperometric methods of determination of ATN have also been developed which focuses on the utilization of flow and batch injection analysis. Some potentiometric sensors based on utilizing ion selective

electrodes have been discussed. These electrodes are very simple to construct and usually are made from polymeric membranes as discussed. Fast response, excellent selectivity, repeatability and reproducibility make the electrochemical sensors discussed in this mini review for analysis of ATN in urine, serum and pharmaceutical formulations, can act as a prospective tools The carbon based bare and modified electrodes discussed in this mini review demonstrates a fast electro oxidation and determination of ATN at the electrode surface modified with various nano materials. On the basis of these methods discussed, progression in this field can be used to develop an automatic electrochemical sensor for the determination of ATN, which is fast, low cost, good performance, very simple, highly sensitive and selective in nature.

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