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Review

Electrochemical Determination of Flutamide, a Non-steroidal Antiandrogen Prescribed in Prostate Cancer

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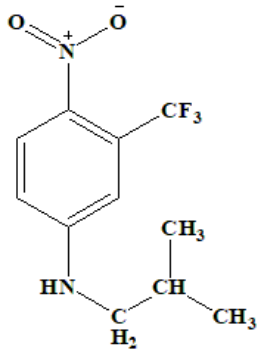
Abstract- Flutamide (4-nitro-3-trifluoromethyl-isobutylanilide) is a synthetic anti-androgenic pharmaceutic compound used in the treatment of prostate cancer. Flutamide is also on the essential drug list of WHO. Determination of flutamide levels in biological fluids or in pharmaceutical dosage is of great importance in clinical medicine. Monitoring flutamide can be done through several sensitive analytical methods such as chromatography, chemiluminescence, spectrophotometry. Since flutamide is an electroactive material, it can be targeted for electroanalysis too. Meanwhile, electrochemical methods are more attended by researchers due to their desirable properties compared with other analytical methods. Designing sensors and biosensors for electroactive drugs may be a new trend in pharmaceutical analyses. Here, the electrochemical methods reported on the determination of flutamide are reviewed. Materials and nanomaterials used in the modification of the working electrodes and the characterization of each method are considered and compared.

Keywords- Flutamide; Voltammetric methods; Nanomaterials; Modified electrodes; Sensor

1. INTRODUCTION

Flutamide (FLU), Eulexin (a brand name), is a synthetic acetanilide, belonging to cytostatic drugs which are a vast group of teratogenic, mutagenic, carcinogenic, and pharmaceuticals to be used in cancer treatment. FLU is a non-steroidal and powerful orally active anti-androgen (anti-testosterone) compound with the chemical name of 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide [1]. Flutamide is one of the chemotherapeutic drugs, widely used for the treatment of prostate cancer. It interacts with DNA of fast-growing cells and prevents them from reproducing. Since flutamide structure is similar to testosterone, it can attach to the receptors of the cancerous cells to block the binding of the testosterone hormone. Flutamide is used as an antineoplastic and antiandrogen medication [2]. Flutamide is in fact a pro-drug and can be changed to a more active form, hence, measurement of its level is important [3].



Scheme 1. Flutamide (FLU) Chemical structure

FLU (Scheme 1) is a light-yellow crystalline powder which is practically insoluble in water and freely soluble in acetone and alcohol. FLU and its active metabolite, 2-hydroxyflutamide can be considered a selective competitor for the androgen receptors that compete with some androgens like testosterone and dihydrotestosterone [4,5] leading to the impairment of testosterone signaling. Actually, FLU blocks the effects of testosterone, which is a natural hormone that stimulates the growth and spread of prostate cancer cells, thus it inhibits their effects and prevents the growth of prostate cancer cells [6]. The prostate cancer cells are not able to grow without the testosterone hormone [7]. Although FLU does not cure prostate cancer, it can control it for several years.

Furthermore, it is also used to treat excess androgen levels in women with polycystic ovarian syndrome [8,9].

After an oral administration by a human, FLU is rapidly metabolized and its hydroxylated metabolites such as 2-hydroxyflutamide and 3-trifluoromethyl-4-nitroaniline form. It principally excretes in urine and lesser extent in feces (4.2%) as an unchanged drug and mainly 2-hydroxyflutamide and 3-trifluoromethyl-4-nitroaniline [10]. Another metabolite of FLU is

4-nitro-3-fluoro-methyl aniline. FLU also has several toxic metabolites including methemoglobinemia, hemolytic anemia, and cholestatic jaundice in both animals and humans after FLU administration.

Flutamide commonly has the following side effects; black and tarry stools, bloody or cloudy urine, continuing diarrhea, continuing stomach pain, difficult, burning, or painful urination, frequent urge to urinate, pale skin, troubled breathing with exertion, unusual bleeding or bruising, unusual tiredness or weakness [11]. A high dosage of FLU in humans causes some symptoms e.g., inflamed prostate, blood in urine, rectal bleeding, hot flashes, loss of sexual interest/ability, tearing of the eyes, diarrhea, nausea, vomiting, enlarged growth of male breasts, drowsiness, liver malfunction, shakiness and unsteady walk, weight loss, sudden sweating and methemoglobinemia [12,13]. Its drug-drug interaction is still a challenging issue. Also, some of their metabolites can retain in some organs [14].

2. FLUTAMIDE DETERMINATION IN BIOLOGICAL FLUIDS

The importance of the biological effects of FLU and its excessive consumption has recently attracted growing scientific interest. Finding a simple, sensitive, and selective method for the determination of FLU that possesses acceptable selectivity and sensitivity in the matrix of real samples is essential. Monitoring pharmaceutical formulations in the pharmaceutical industry are important as well as ensuring the safety of the people who encounter them.

Up to now, several analytical methods are employed for the analysis of FLU in various samples, including mass detector [15], gas chromatography [16], high-performance liquid chromatography [17-21], spectrophotometry [22-24], chemiluminescence [25] and fluorescence [26]. Each method has some advantages and also suffers from different problems and drawbacks.

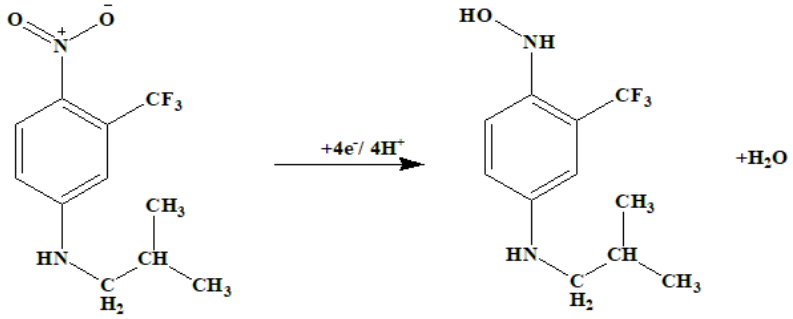
In recent years, considerable efforts have been made toward improving analytical methods. Electroanalytical techniques have been proven to be excellent alternatives for the fast determination of pharmaceuticals in simple or even complex matrixes [27-36]. Because they have low-cost instrumentation, simple operation, and adaptable analytical tool with outstanding detection, high sensitivity, reproducibility, ease of miniaturization, fast response time, specific selectivity of target molecules, and without the need for derivatizations or time-consuming extraction steps [37,38]. Therefore, they are used for many important applications in clinical, pharmaceutical, industrial, and environmental analyses. However, the development of an electrochemical method with improved analytical parameters such as selectivity, sensitivity, and stability, depends on the used materials on the solid surface of the working electrode.

In this regard, we are going to review the electrochemical methods reported on the determination of flutamide in various biological samples. Materials and nanomaterials used in the modification of the working electrodes and the characterization of each method are considered and compared.

3. ELECTROANALYTICAL DETERMINATION OF FLUTAMIDE

Considering the electroactive structure of FLU, it has been a target molecule in several electrochemical studies. A literature survey reveals that there are about 42 reports on the electro-determination of FLU in various biological fluids, pharmaceutical and environmental samples [39-79]. Table 1 lists these research works and compares their important features including the type of working and reference electrodes, the used electrode modifiers, the applied electrochemical technique, the type of real samples to be analyzed, linear range, and detection limits.

The first study dates back to 1989 when a polarographic reduction of flutamide by direct current polarography (DCP), alternating current polarography (ACP), normal pulse polarography (NPP), and differential pulse polarography (DPP) was done by Snycerski et al [39]. The results of the work showed that DCP was the best method for electroanalysis of FLU. NO_2 group on the benzene ring of the molecule was reduced through a four-electron transfer mechanism at potentials of -0.48 to -0.56 V.



Scheme 2. Elecro-reduction mechanism of flutamide

Álvarez-Lueje et al [40] in 1998 also studied the flutamide reduction on a dropping mercury electrode (DME). The nitroaromatic moiety of FLU is reduced through an electrochemical process.

Hammam et al [41] in 2004 optimized three adsorptive cathodic stripping voltammetric procedures for the determination of flutamide in bulk, tablets, and human serum by applying linear-sweep (LS), differential-pulse voltammetry (DPV), and square-wave voltammetry (SWV). The results showed that SWV was more reliable for the determination of FLU in low concentration levels.

Long after in 2011, Pecková et al [42] optimized conditions for direct current and DPV determination of FLU and its main metabolite 4-nitro-3-trifluoromethylaniline on a hanging mercury drop minielectrode (HMDME) in Britton-Robinson buffer (BR; pH 12.0)-methanol (9:1). They showed that the method can be used for the determination of FLU in tablets and for the determination of both FLU and 4-nitro-3-trifluoromethylaniline in urine samples.

Brahman et al [43] was able to determined flutamide level on the surface of a polymer film modified carbon paste electrode (CPE) in the presence of cetyltrimethylammonium bromide in pharmaceutical formulation. In the presence of CTAB, the modified electrode showed catalytic activity, high sensitivity, stability and a wide linear range.

Ahmadi et al [44] modified a glassy carbon electrode (GCE) surface and *p*-tert-butylcalix[4]arene and *p*-tert-butylcalix[6]arene and Ag nanoparticles which is synthesized through electrochemical reduction of Ag^{+}. The presence of the calixarene layer on the electrode surface controlled the particle size and prevented agglomeration of Ag nanoparticles (Ag NPs). The modified electrode shows a catalytic ability for the reduction of FLU in pH 6 (Figure 1).

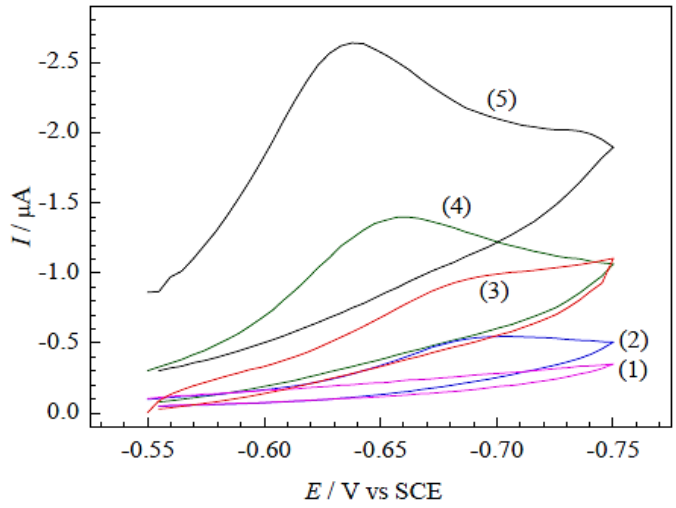


Figure 1. Cyclic voltammograms of bare GCE in the absence (1) and presence of (2) 1.0 mM FLU in 0.1 M PBS at pH 6.0, scan rate 50 mV/s; Cyclic voltammograms of modified GCE (3-5) in the presence of 0.2 mM FLU. Reprint with permission from [44]

Temerk et al [45] in 2015 presented the interaction of FLU with single and double stranded DNA at different temperatures at physiological pH 7.4. Cyclic voltammetry (CV), SWV and UV-visible spectroscopy were used to monitor the FLU interaction with DNA sequences. The results showed that FLU can intercalated between dsDNA bases and the strength of the interaction is independent on the ionic strength.

In another work in 2016 reported by Brahman et al [46], differential pulse voltammetry (DPV) was applied for electro-analytical reduction of FLU. The reduction peak current of FLU on a bare carbon paste electrode (CPE) can be seen in Figure 2. The modified electrode with d-DNA showed catalytic activity, high sensitivity, stability and wide linear range due to the strong interaction of FLU with guanidine moieties of DNA molecule.

The next research mainly deals with the application of cleanup, preconcentration and electrochemical determination of flutamide. A new system was developed by Ensafi et al [47]

to cleanup and detect flutamide at the surface of a pencil graphite electrode (PGE) functionalized with thiol groups as a working electrode. DPV was the detection technique. The surface of the PGE was coated with sodium dodecyl sulfate (SDS)-modified silica thin film. FLU is first extracted from sample matrix to the modified silica thin film and then reduced electrochemically, next, it was oxidized at the electrode surface. The extraction system and DPV was successfully used for the determination of FLU in human urine and plasma samples.

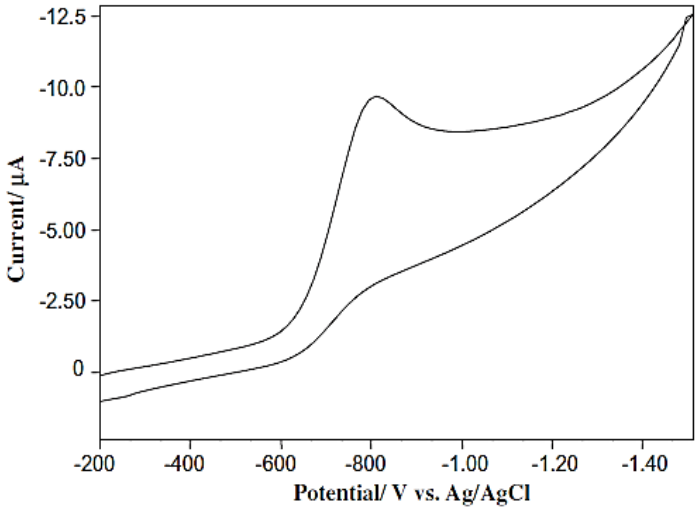


Figure 2. Cyclic voltammogram of FLU in 0.3 M phosphate buffer (pH=7), at bare CPE with scan rate of 50 mV/s; Reprinted with the permission from [46]

In 2016, Temerk et al [48] developed a sensitive electrochemical method based on square wave cathodic adsorptive stripping voltammetry (SWCASV) using PGE for the simultaneous determination of FLU and irinotecan in bulk form, human urine and serum samples.

In a report in 2017 by Banerjee et al [49], Ag NPs decorated on reduced graphene oxide (rGO-Ag) was applied as electrode modifier for the electrochemical detection of FLU. A current peak at potential of -0.07 V in the voltammogram indicated the catalytic reduction of NO_2 group of FLU by rGO-Ag.

Brahman et al [50] modified a carbon paste electrode surface by ferrocene (FC) and multiwalled carbon nanotubes (MWCNTs) and used it as a highly sensitive electrochemical sensor for the determination of FLU in serum, plasma and urine samples. Electrochemical impedance studies showed good conductivity of the modified electrode.

Ensafi et al [51] in 2017 reported a biosensor made of a screen-printed electrode (SPE) modified by reduced graphene oxide (rGO) and decorated with ds-DNA (Figure 3). The proposed biosensor was applied via the interaction of salmon sperm ds-DNA molecule with FLU. The oxidation currents of guanine and adenine were applied as electrochemical probes.

Through the interaction of FLU with the DNA, the oxidation currents of guanine and adenine weakened at the ds-DNA/rGO/SPE surface detecting by DPV technique.

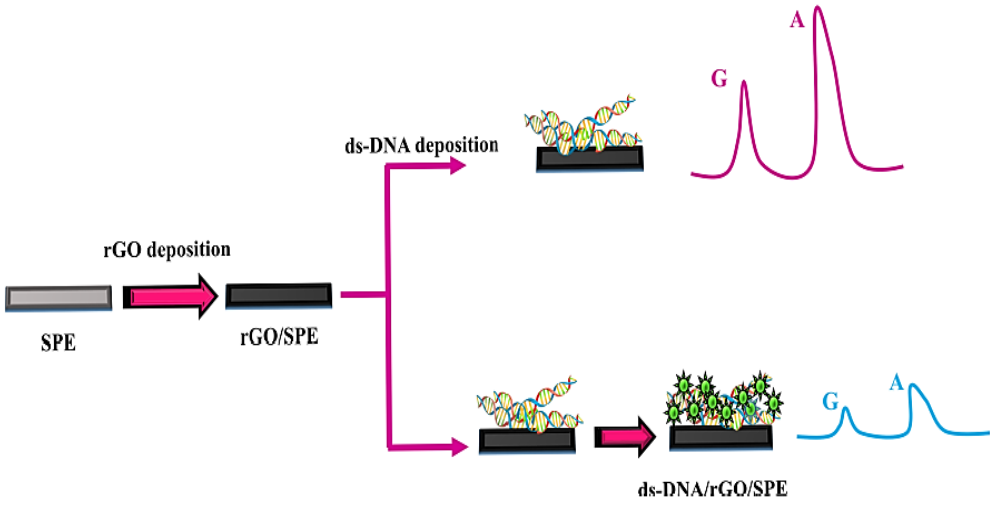


Figure 3. Schematic of a designed biosensor for FLU detection made of a screen-printed electrode (SPE) modified by reduced graphene oxide (rGO) and decorated with ds-DNA [51]

Farias et al [52] also determined FLU by modification of a GCE with functionalized multiwalled carbon nanotubes (MWCNTf). The modified electrode showed high catalytic activity, high sensitivity, and high stability and was applicable over a wide concentration range for FLU. The results showed that this electrode presented the best square-wave voltammetric response to FLU in Britton–Robinson buffer solution at pH 5.0 at frequency of 50 Hz and amplitude of 0.06 V.

In another report in 2017, Karthik et al [53] developed an electrochemical sensor made of graphene oxide (GO) modified on a glassy carbon electrode (GCE). The proposed sensor has good repeatability, reproducibility, stability and selectivity in the presence of biologically co-interfering substances.

Švorc et al [8] in 2017 introduced an advanced, fast and simple electrochemical method for the detection of FLU. The method was designed by coupling of DPV and SWV techniques with a boron-doped diamond (BDD) working electrode in 0.1 M sulphuric acid as the supporting electrolyte. The voltammogram of FLU showed three irreversible and diffusion-controlled oxidation peaks at +1.1, +1.4 and +1.9 V (Figure 4).

In another report in 2018, Rezaeifar et al [54] developed a sensitive voltammetric sensor using hyperbranched polyglycerol functionalized-graphene oxide, and ionic liquid mediated hollow fiber-pencil graphite electrode (HF/HBP-GO/PGE) for the determination of FLU. A two-centimeter piece of porous polypropylene hollow fiber membrane was impregnated with ionic liquid (1-pentyl-3-methylimidazoliumbromide), and a graphite rod modified with hyper branched polyglycerol/graphene oxide (HBP-GO), was placed inside the fiber lumen. The

proposed electrode shows good activity, sensitivity, stability over a wide range of concentration of FLU.

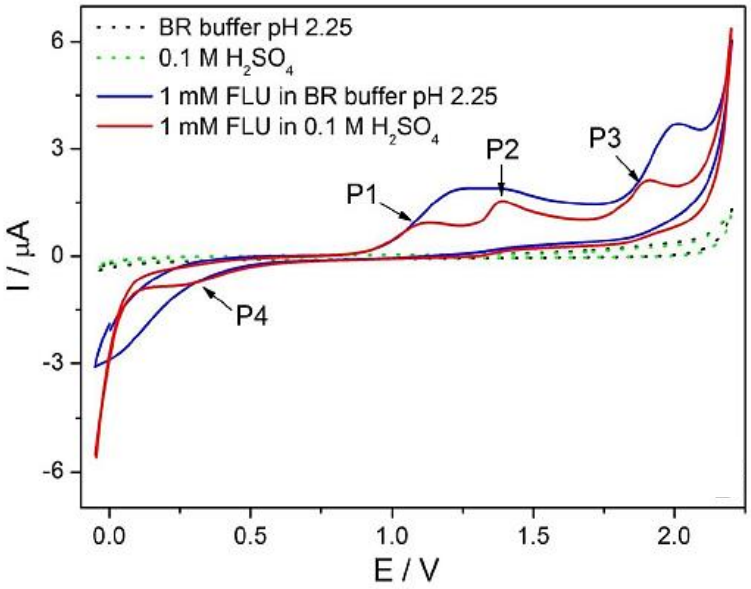


Figure 4. Voltammograms of blank and 1 mM FLU in 0.1 M H_2SO_4 and BR buffer pH 2.25 and related oxidation peaks (P1, P2, P3 and P4) on the BDD electrode (scan rate: 100 mV/s); Reprinted with permission from [8]

In 2019, Mutharani et al [55] prepared chitosan-gold collapse gel (CS-Au CG) through reduction of the chloroauric acid ($HAuCl_4$) with a polysaccharide and chitosan (CS). CS-Au CG was then employed as a sensing platform for efficient one-step electrochemical deposition of poly(bromophenol blue) (PBPB) redox mediator on a GCE surface. The proposed electrochemical sensor showed acceptable linear range and sensitivity (0.63 $\mu A \mu M^{-1} cm^{-2}$) in the determination of FLU in biological samples.

In two others reports in 2019 a bare Au electrode [56] and a GCE modified by reduced graphene oxide decorated CuO [57] were also used for FLU determination.

Afzali et al [58] in 2020 investigated electrochemical behavior of FLU using a carbon paste electrode (CPE) modified by CuO nanoparticles/graphene oxide/polyaniline (CuO/GO/PANI) nanocomposite.

In another work in 2020, Akilarasan et al [59] used cerium ortho-vanadate nanorods ($CeVO_4$-NRs) for modification of a glassy carbon electrode. The catalytic ability of the proposed nanomaterials caused a high sensitivity of the electrode and reduce the detection limit.

Using various nanomaterials for the modification of the electrodes mostly glassy carbon electrode was the trends in 2020 and 2021. Magnetic nickel-ferrite oxide nanoparticles decorated reduced graphene oxide ($NiFe_2O_4$/rGO) [60], nanoacetylene black [61], graphitic-

carbon nitride (g-C_3N_4) [62], N-CQD@Co_3O_4/MWCNT hybrid nanocomposite [63], α-$ZnMoO_4$ nanospheres [64], Au nanoparticle-reduced graphene oxide/polypyrrole nanocomposite [65], lanthanum cobaltite decorated halloysite nanotube nanocomposite [66], graphene quantum dots and lanthanum doped zirconia nanoparticles [67], perovskite type calcium titanate interfacial nanostructure supported on graphene oxide sheet [68], Co_3O_4 nanoparticles embedded N-doped porous carbon [69], cabbage flower-like Ho^{3+}/NiO nanostructure [70], Sn-doped ZnO hexagonal micro discs anchored on rGO [71], polyhedral oligomeric silsesquioxane [72], manganese oxide/hexagonal boron nitride nanocomposite [73], iron vanadate nanostructures [74], iron-cobalt oxide/polypyrrole nanocomposite [75], gold nanoparticles [76], ZnO-Co_3O_4 capped on carbon nitride nanomaterials [77], $ZnMn_2O_4$ nanoparticles decorated porous reduced graphene oxide [78] were all reported as novel modifiers for electrochemical determination of FLU in mainly human serum and urine sample. In all cased pH 7 (phosphate buffer) was used as a cell electrolyte.

Among these reports, there is a report which is different and interesting [79]. In this work, a selective and sensitive electrochemical sensor was introduced for FLU determination. The sensor was made of FLU molecularly imprinted polymer which was electrochemically synthesized on a GCE pre-modified by rGO decorated Au nanoparticles (Figure 5). The used monomer was 2-aminophenol.

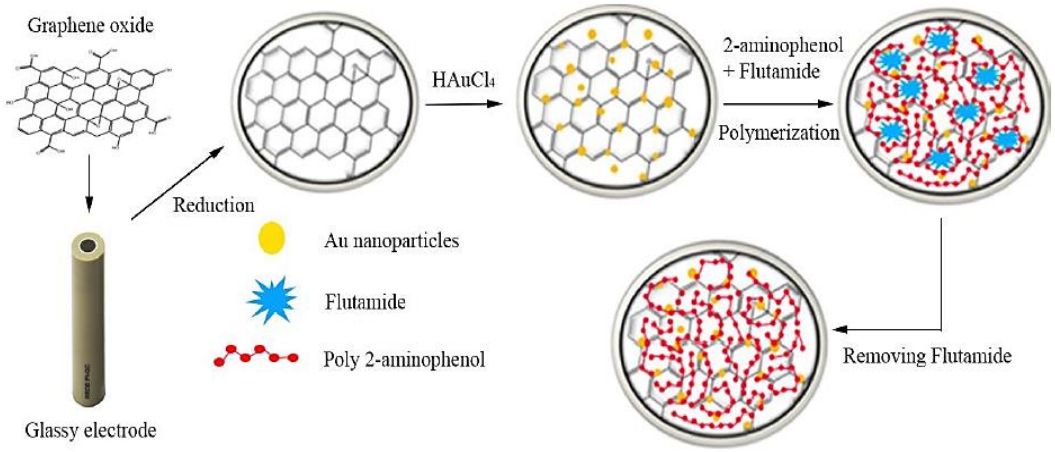


Figure 5. Schematic of MIP based FLU sensor [79]

The prepared sensor showed very good stability, and analytical performance in analysis of FLU. The proposed sensor was successful in analysis of FLU in environmental water and urine samples. The results showed that the sensor was selective toward FLU in comparison with other similar nitro containing compounds.

Table 1. Electroanalytical reports on flutamide determination and their features

Working and Ref Electrodes	Electrolyte and pH	Tech.	Real sample	Linear Range	LOD	Year
DME *vs.* SCE	0.1 N PBS pH 7.05	DCP, DPP, ACP, NPP	Tablet	3.6×10^{-7} -3.6×10^{-6} M	-	1989 [39]
DME *vs.* Ag/AgCl	0.04 M BR[1]/ 0.1 M KCl pH 8.0	DPP	Tablet	1.9×10^{-6} -1×10^{-3} M	-	1998 [40]
DME[2] vs. SCE	Acetate buffer pH 5	DPV LSV SWASV[3]	Tablet	5×10^{-7} –6×10^{-6} M 4×10^{-7} –5×10^{-6} M 5×10^{-8} –1×10^{-6} M	1.9×10^{-7} M 8.7×10^{-8} M 9.7×10^{-9} M	2004 [41]
HMDmE[4] *vs.* Ag/AgCl	BR pH 12.0	DCV DPV	Tablet	2×10^{-7}-10×10^{-5} M 2×10^{-7}-10×10^{-5} M	0.3×10^{-8} M 1.5×10^{-8} M	2011 [42]
Polymer film modified CPE *vs.* Ag/AgCl	0.3 M PBS pH 7.0	DPV	Pharmaceutical formulations	20-160 mg/L	50 ppb	2012 [43]
Ag NPs/MGCE *vs.* SCE	0.1 M PBS pH 6.0	DPV	Tablet	10-1000 µM	9.33 µM	2015 [44]
HMDE *vs.* Ag/AgCl	0.2 M PBS pH 7.0	SWV	Clinical samples	6.60×10^{-7}– 4.45×10^{-6} M	1.87×10^{-7} M (ssDNA) 4.27×10^{-7} M (dsDNA)	2015 [45]
ds-DNA modified CPE *vs.* Ag/AgCl	0.3 M PBS pH 7.0	DPV	Pharmaceutical formulations	20–160 ppm	1.0 ppm	2016 [46]
SDS-PGE *vs.* Ag/AgCl	0.04 BR pH 2.5	DPV	Human urine and plasma	0.10–100.0 nM 0.10–100.0 µM	34 pM	2016 [47]
PGE *vs.* Ag/AgCl	80 mM BR pH 5.0	SWCASV	Bulk form, human urine and serum samples	3.98×10^{-7}-6.36×10^{-6}	1.55×10^{-8}M	2016 [48]
rGO-Ag modified PGE *vs.* Ag/AgCl	-	SWV	Pharmaceutical tablets, biological samples	0.1 - 0.3 mM	1.16 µM	2017 [49]
FC/MWCNTs/CPE *vs.* Ag/AgCl	0.2 M acetate buffer pH 4.5	SWV	Serum, plasma and urine	0.1 - 110 µM	0.001 µM	2017 [50]
ds-DNA/rGO/SPE *vs.* Ag/AgCl	Acetate buffer pH 4.8	DPV	-	0.0025–0.0750 and 0.0750–7.5000 nM	1.5 pM	2017 [51]
MWCNTf/GCE *vs.* Ag/AgCl(sat.)	0.1 M BR pH 5.0	SWV	Pharmaceutical formulations, artificial urine samples	0.1- 1000 µM	0.03 µM	2017 [52]
GO/GCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	LSV	Rat brain, kidney and human blood serum	0.009 - 1.9 µM,	6 nM	2017 [53]
BDD[5] *vs.* Ag/AgCl	40 mM BR pH 2.25	DPV SWV	Pharmaceutical formulations, spiked human urine and water samples	0.99–42.9 µM 4.8–35.5 µM	0.42 µM 0.18 µM	2017 [8]
HF[6]/HBP[7]-GO/PGE *vs.* Ag/AgCl	0.04 M PBS pH 8.0	DPV	Human plasma	0.1–110 µM	0.029 µM	2018 [54]
CS-Au NPs/poly (bromophenol blue)/ GC/ *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	Human urine and blood serum	0.01–1245 µM	4.8 nM	2019 [55]

[1] Britton-Robinson (BR)
[2] Dropping Mercury Electrode (DME)
[3] Square-wave adsorptive stripping voltammetry
[4] Hanging Mercury Drop mini electrode
[5] Boron Doped Diamond
[6] Hallow fiber
[7] Hyperbranched polyglycerol

Au *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	-	6-60 μM	1.8 μM	2019 [56]
rGO-CuO/GCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	Amperometry	Human serum	0.005-71.32 μM	0.001 μM	2019 [57]
CuO/GO/PANI/CPE *vs.* Ag/AgCl	0.1 M PBS pH 7.0	SWV	Human urine and pharmaceutical samples	0.050 - 200.0 nM	14.0 pM	2020 [58]
$CeVO_4$-NRs[8]/GCE *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	Human urine and blood serum	0.01-57 μM	1.94 nM	2020 [59]
$NiFe_2O_4$/rGO/ GCE *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	Human urine and blood serum	0.24–40.00 μM	0.05 μM	2020 [60]
nano-AB/GPLE[9] *vs.* Ag/AgCl	0.1 M PBS pH 7.0	SWAdCSV[10]	Tablet	0.026-0.477 μM	1.39 nM	2020 [61]
g-C_3N_4/ GCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	DPV	Environmental samples	2-1208 μM	0.05 μM	2020 [62]
N-CQD@Co_3O_4/ MWCNTs/ GCE *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	Human urine	0.05 – 590 μM	0.0169 μM	2020 [63]
α-$ZnMoO_4$ nanospheres/GCE *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	Human urine	0.1-73 μM	33 nM	2020 [64]
AuNP@rGO/PPy/ GCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	DPV	Human blood serum	0.01-1080.11 μM	2.3 nM	2020 [65]
LCO/HNT[11]/GCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	DPV	Environmental samples	0.009–145 μM	0.002 μM	2020 [66]
GQDs@ La^{3+}@ZrO_2/ GCE *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	Human urine	0.00175-15.75 μM	0.00082 μM	2020 [67]
GOS/$CaTiO_3$ NC/ GCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	Amperometry	Human urine and blood serum	0.015-1184 μM	5.7 nM	2020 [68]
Co_3O_4@NPC[12]/GCE *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	Human urine	0.5 to 400 μM	12 nM	2021 [69]
Cabbage flower-like Ho^{3+}/NiO nanostructure/ GCE *vs.* SCE	0.1 M PBS pH 7.0	DPV	Tablets and urine	0.01 to 400.0 μM	5.7 nM	2021 [70]
Sn-ZnO/rGO GCE *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	Human urine and river water	0.01 to 170 μM	7.3 nM	2021 [71]
POSS-S-Au[13]/ *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	Drinking and tap water	3-30 μM	0.12 μM	2021 [72]
Mn_2O_3@h-BN[14]/ GCE vs. Ag/AgCl	0.05 M PBS pH 7.0	DPV	Human urine	0.08 to 1940 μM	0.008 μM	2021 [73]
$FeVO_4$/GCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	DPV	Human blood serum	0.06 to 777.46 μM	0.054 μM	2021 [74]
FCO/PPy/ SPCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	DPV	Human urine and blood serum	0.4 μM to 376 μM	0.086 μM	2021 [75]
AuNPs/GCE *vs.* Ag/AgCl	0.1 M PBS pH 7.0	DPV	Cell culture media containing prostate cancer cells	1–600 μM	1.5 nM	2021 [76]
ZnO-Co_3O_4@C_3N_4/ GCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	DPV	Human urine and blood serum	0.01–98.6 μM	0.00373 μM	2021 [77]
$ZnMn_2O_4$-Porous GO/ GCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	DPV	Human urine	0.05 - 3.5 μM	8 nM	2021 [78]
MIP/rGO-Au NPs/GCE *vs.* Ag/AgCl	0.05 M PBS pH 7.0	DPV	Human urine and river water	0.007-1.36 μM	2.9 nM	2021 [79]

[8] Cerium orthovanadate nanorods
[9] Nanoacetylene black coated the surface of graphite pencil lead electrode
[10] Square wave adsorptive cathodic stripping voltammetry
[11] lanthanum cobaltite decorated halloysite nanotube
[12] Nano porous carbon
[13] gold modified Polyhedral Oligomeric Silsesquioxane
[14] Manganese oxide supported on hexagonal boron nitride

4. CONCLUSION

Flutamide (FLU) is a non-steroidal anti-androgen drug that has a specific anti-androgenic activity which is used in the treatment of prostate cancer. It functions by interfering DNA in fast growing cells and preventing them from reproducing. FLU may also be used to treat excess androgen levels in women. The chemical structure of FLU shows an aromatic nitro-group which can be electrochemically reduced to amino-group through a four-electron transfer mechanism. Hence, some researchers studied this phenomenon on the various electrode surfaces in different conditions during the years. Among them, Ensafi et al [47] reached the best detection limit (1.5 pM) using differential pulse voltammetry at ds-DNA/rGO modified screen printed electrode in acetate buffer solution pH 4.8. Two more researches reported detection limits in the same order, 34 pM by Ahmadi et al [44] and 14.0 pM by Afzali et al [58]. Most of researchers evaluated their work in pharmaceutical formulation, blood plasma or serum and urine samples. Karthik et al [53] and Mehrabi [76] innovatively evaluated their research in rat brain and kidney samples and cancer cell culture. Studies which have been done during the recent years have mostly focused on introducing a nanomaterial or a nanocomposite as novel electrode modifiers to decrease the limit of detection and increase the sensitivity of the working electrodes. DPV was the predominant technique used in most of the studies. In the most of researches reported synthesis and characterization of the used nanomaterials have been bolded and mechanism of the responses and the performance of the electrode in real world of analysis has lesser role. The important point which should be noted and considered more in the future studies may be the cost and price of the used materials and analytical performance of the designed sensor.

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