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REVIEW ARTICLE

Cyclodextrins Based Electrochemical Sensors for Biomedical and Pharmaceutical Analysis

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Abstract: Electrochemical sensors are very convenient devices, as they may be used in a lot of fields starting from the food industry to environmental monitoring and medical diagnostics. They offer the values of simple design, reversible and reproducible measurements, as well as ensuring precise and accurate analytical information. Compared with other methods, electrochemical sensors are relatively simple as well as having low costs, which has led to intensive development, especially in the field of medicine and pharmaceuticals within the last decade. Recently, the number of publications covering the determination of amino-acids, dopamine, cholesterol, uric acid, biomarkers, vitamins and other pharmaceutical and biological compounds has significantly increased. Many possible types of such sensors and biosensors have been proposed: owing to the kind of the detection-potentiometric voltametric, amperometry, and the materials that can be used for, *e.g.* designing molecular architecture of the electrode/solution interface, carbon paste, carbon nanotubes, glass carbon, graphite, graphene, PVC, conductive polymers and/or nanoparticles. The active compounds which provide the complex formation with analyte (in the case of non-current techniques) or activate biomolecules electrochemically by particle recognition and selective preconcentration of analyte on the electrode surface (in the case of current techniques) are the most recently used cyclodextrins. These macrocyclic compounds have the ability to interact with a large diversity of guest particles to form complexes of the type of guest host, for example, with particles from drugs, biomolecules, through their hydrophilic outer surface and lipophilic inner cavities. Cyclodextrins have been the subject of frequent electrochemical studies that focused mostly on both their interactions in a solid state and in solution. The process of preparing of CDs modified electrodes would, consequently, open new avenues for new electrochemical sensors and, therefore, widen their use in biomedical and drug analysis.

This review presents information on manufacturing techniques and performances of these sensors and biosensors. The opportunities for these sensors to carry out biomedical and pharmaceutical researches are demonstrated.

Keywords: Electrochemical sensors, electrochemical biosensors, potentiometric electrode with cyclodextrin, voltametric electrode with cyclodextrin, biosensor modified with cyclodextrin, potentiometric sensor with cyclodextrin, voltametric sensor with cyclodextrin, amperometry sensor with cyclodextrin, pharmaceutical analysis, biomedical analysis, cyclodextrins, modified electrodes.

1. INTRODUCTION

The field of chemical sensors (biosensors) modified with cyclodextrins has been a growing research area and a wide range of papers have been published in this field over the last decade (Figs. **1** and **2**). The electrochemical sensors are effectively applied for the quantitative indication of the pharmaceuticals and biomolecules in complex samples such as biological fluids and tablets. The sensors provide many benefits of a simple design: reversible and reproducible measurements, ensuring precise and accurate analytical information, plus a long range of linearity, low detection limit, good se-

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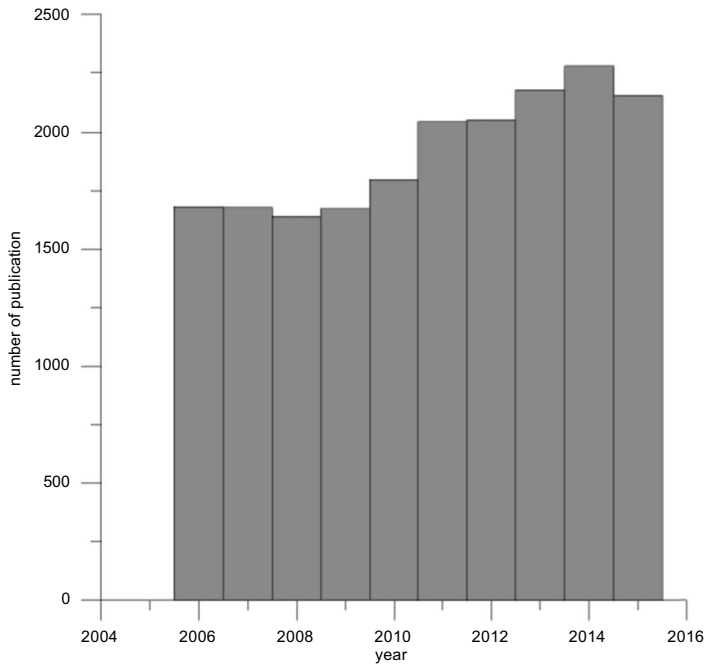

Fig. (1). A diagram of the number of publications using cyclodextrins, in a period covering the last 10 years.

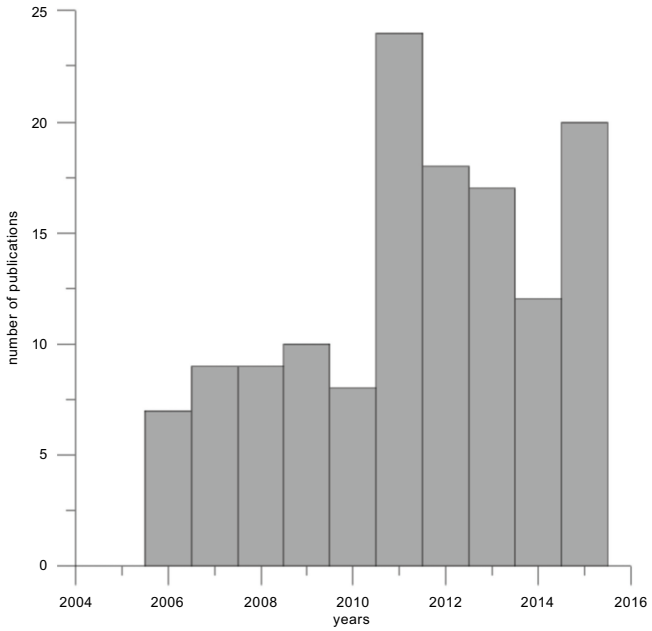

Fig. (2). A diagram of the number of publications concerning the modified cyclodextrins electrochemical sensors and biosensors for pharmaceutical and biomedical applications in a period covering the last 10 years.

lectivity, as well as their relatively simple and low cost, which has led their intensive development.

Thanks to the remarkable properties of cyclodextrins, they have been studied extensively as a model of molecular recognition, inclusion complexes formations or selective pre-concentration of the analyte at the electrode surface. They have an increasing interest as modifiers of many electrochemical sensors; they can improve the double selectivity of the membrane electrodes to the discrimination of the enantiomers and they have the activity as modifiers of organic electrode reactions. In the many researches, it has been proven that the β -CDs content in the electrode could considerably affect the peak currents of organic molecules.

This review has put special emphasis on to some chosen kinds of cyclodextrins modified sensors, used

(voltametricly and potentiometricly) in pharmaceutical and biomedical analysis.

The state of the development of sensors and biosensors has been based, in the recent literature, on the following trends:

1. The development, testing and applicability of new types of carbon paste modified with cyclodextrins electrodes.

   Simple forms of graphene moieties are replaced with modern carbon materials such as single-walled-carbon nanotubes, carbon fibres, graphene, carbon paste screen - printed electrodes modified with thin films of the β-CDs.

   Recently, the most used in electrochemical sensors are carbon nanomaterials (CN, SWCNT, and MWCNT) with a cylindrical structure. They have been studied as a material for the construction of sensors aiming to improve their analytical response. Carbon nanotubes have unique properties: high electrical conductivity, mechanical resistance, narrow distribution size, high accessible surface area and chemical stability. Therefore, they provide a stable, faster electron transfer between the electrode and electro-active species in the solution. Consequently, the electrochemical sensors and biosensors are characterised by better analytical parameters *e.g.* better stability, selectivity and detection limit. Graphene oxide is also successfully used for fabrication *i.e.* of biosensors. It has properties such as a high mechanical strength, a very large surface area, a tunable band gap, high thermal conductivity and elasticity. This nanomaterial functions as an "electron wire" between the electrode surface and the redox centres of the enzyme or protein molecules, providing for the creation of GO/protein complexes in biosensors.

2. The creation highly selective and sensitive chemical and biochemical sensors based on functionalised β-cyclodextrin nanomaterial (*e.g.* the nanoparticles of Au, coated with cyclodextrins), serving as a scaffold for molecular recognition. Metalnanoparticles (*i.e.* Au, Ag, Cu and Co) improved sensitivity and stability of these sensors through their excellent properties: high electrical conductivity, chemical stability and biocompatibility.

3. The preparation of insoluble polymeric films (pre-CDP), having a very good film forming ability, as compared with the CD modified electrode mixture and CD pre-CDP modified electrodes, is more stable.

4. The applicability of lipophilic cyclodextrins in plasticised membranes is used especially in potentiometry. The modification of cyclodextrins, which is based on the alkylation of hydroxyls in positions 2, 3, 6, results in more lipophilic capabilities of cyclodextrins, thanks to which they can be used as active compounds in the organic membranes of electrodes and they can interact with other molecules of compounds, for example drugs.

2. SENSORS, BIOSENSORS, CHARACTERISTICS

2.1. General Working Principle

A chemical sensor, according to the definition of IUPAC [1], "is a device that transforms chemical information, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal. The chemical information can originate from a chemical reaction of the analyte or from a physical property of the system investigated. Chemical sensors contain two basic functional units: a receptor part and a transducer part. Furthermore, some sensors may include a membrane as a separator. In the receptor part of a sensor, the chemical information is transformed into a form of energy which may be measured by the transducer. The transducer part is a device capable of transforming the energy carrying the chemical information about the sample into a useful analytical signal."

Because of the receptor type, the sensors can be divided into chemical (chemical sensors) and biological (biosensors).With respect to chemical sensors, the receptor (chemical molecules, ions) interacts with the analyte. As regards biosensors, an analyte interacts with the biological receptor which is the enzyme, generally isolated or contained in the tissues or microorganisms (enzymatic biosensors), or bodies and antibodies forming elements of the immune system (immunosensors) or biological membranes. According to IUPAC recommendations, biosensors are classified as chemical sensors. The difference is the kind of generating analytical chemical signal coming from any type of chemical reaction.

"Electrochemical devices transform the effect of the electrochemical interaction analyte - receptor into a useful signal. Such effects may be stimulated electrically or may result in a spontaneous interaction at the zero-current condition. The following subgroups may be distinguished: voltametric sensors including amperometry devices and potentiometric sensors."[1].

"Potentiometric sensors, in which the potential of the indicator electrode (ion-selective electrode, is measured against a reference electrode," [1] at zero current (I = 0). The electrode phenomena take place without the signal of potential excitation. The principle of the activity of ion-selective electrodes is the ion transport of analyte from the sample solution to the membrane electrode. This causes a potential difference across the membrane and produces a so-called membrane potential, which depends on the negative logarithm of the ion activity (concentration) ion for which the electrode is most selective (E = f (c)). In addition, the characteristic of the electrode response includes a number of frequently measured parameters: selectivity, response time, operative response range, temperature dependence of response, and operative lifetime, among the more important [2].

Voltametric sensors and amperometry devices, in which the electrode phenomena occur with the use of the excitation signal. The current is measured at a constant potential (E = const.) and it depends on the analysed sample concentration (I = f (c)) in the case of amperometry sensors. Voltametric sensors are characterised by the use of the alternating excitation signal (the signal is characterised by increasing amplitude).

As a result of the redox processes occurring at the electrode, followed by measuring of the current flowing through the electrode, which depends on the applied potential (I = f (E)) with c = constant.

This subgroup (according to IUPAC [1]) may include sensors based on chemically inert electrodes, chemically active electrodes and modified electrodes. In this group sensors with and without (galvanic sensors) external current source are included.

2.2. Recent Trends in the Design of Electrochemical Sensors

In the last ten years, there has been a development of voltametric, amperometry and potentiometric sensors applicable in biomedical science, and a lot of various trends have been reported in this area. The modified electrochemical sensors, especially with solid contact, have been commonly introduced. The diverse number of materials, such as carbon nanotubes, metal oxides, conducting polymers and inorganic catalysts, are used to modify the surfaces of the electrodes. Recently, a very popular carbon material with unusual properties, multiwalled carbon nanotubes (MWCNTs), is used to ensure the electron transport between electroactive species and the electrode. [3-5].

Lately, the main trend in the design of the sensor is to eliminate the internal solution (in the case of potentiometric electrodes) and a solid contact ion selective electrodes SCISE-s, containing a different surface of electron conductivity *e.g.* gold, carbon, platinum, or an Ag/AgCl electrode immersed in a polymer system, have been developed. The solution may be replaced with a conductive polymer, chemical compound with ionic-electron conductivity (SCISE-s). In the other type of coated wire electrodes (CWE), on a metal reference electrode, an all-polymer membrane can be formed directly [6].

The electrodes applied in voltammetry are characterised with a slightly different design. It is the general trend to eliminate the mercury electrodes, replacing them with solid contact electrodes. The voltametric (amperometry) sensors are formed overall from a conductive material, *i.e.* inactive metal conductor (gold, platinum graphite carbon) in the form of glassy carbon, pyrolitic graphite and semiconductors, *i.e.* oxide of indium and tin. This material is most commonly a flat disc, which is arranged in the insulating material (*e.g.* a Teflon rod), with electrical contact- the conductive wire.

Recent achievements and trends in the literature conclude the cyclodextrins modified electrodes. The cyclodextrins represent an attractive promise for the future improvement of electrochemical sensors and biosensors and remain a very active field of research for a wide area of applications in many areas, including pharmaceutical and biomedical analyses [7].

2.3. Electrochemical Sensor Fabrication Methods

Several techniques were used for the construction of cyclodextrin modified electrodes. It was formulated in a lot of carbon paste, glassy carbon-modified with graphene-electrodes by the incorporation of β-cyclodextrins. The second type of modification method consisted in cyclodextrin incorporation in polymeric films. Some of the common methods of modification electrodes are mentioned below [8].

2.3.1. Langmuir-Blodgett (L-B) Technique

The layer-by-layer (LBL) self-assembly technique provides a simple and unsophisticated method for the construction of stable nano-structured thin films [9]. The electrostatic layers are obtained by moving the monolayers from the air-water interface onto solid substrates requiring amphiphilic CD molecules. The (LBL) method is presumed to be one of the most successful techniques for the formation of ultra-thin multilayer films. The layer-by-layer technique can be applied to

prepare multiple CNTs layers with molecule recognition activity on modified glassy carbon electrodes.

To prepare the sensor, the CNTs are initially diffused by β-CD in a water solution, with sonication. Afterwards, the β-CD interacts with the CNTs *via* non-covalent (van der Waals) force to create stable β-CD-CNTs nanostructures. Afterwards, the negatively charged β-CD-CNTs and positively charged molecules of other compounds (chitosan [10], poly (diallyl dimethyl ammonium chloride) PDDA [11]), results in the formation of stable multiple assembled layers on a solid substrate GC electrode. The CNTs nanostructured films assembled by the LBL method provide many evident attributes, such as unusual electro-oxidation properties toward the analyte sample, and high stability.

2.3.2. Self-Assembly Method

Self-assembled monolayers (SAMs) prove an easy way of modifying metal electrode surfaces by cyclodextrin, modified with organo-sulfur compounds (thiols, disulfides, silanes). Cyclodextrins adsorbed on metal electrodes (especially gold) form highly organised monolayers (SAMs). In order to prepare the modified electrode (*e.g.* β-CD-GO/APTMS/GC), the activated glassy carbon electrode was immersed in 3-amino-propyltrimethoxysilane toluene solution, enabling the assembly of the APTMS molecules onto the GC surface and interaction *via* the Si-O-C bond [12]. Then, the APTMS-modified electrode was immersed in a graphene oxide aqueous solution for a limited period. After that, β-CD modified electrodes were prepared according to the procedure described elsewhere [13] by immersing them into an appropriate aqueous solution of cyclodextrins for some time at room temperature. Self-assembled monolayers are capable of passing on the electron and can be used as supports to determine small particles or to immobilise guest-added polymers [14].

2.3.3. Carbon Paste Electrodes Modified with Cyclodextrins

Modified carbon paste electrodes have obtained significant importance in the preparation of sensors, through their residual current and less noise, as well as the fact that they are relatively cheaper and easier to prepare. They have a wide range of cathodic and anodic application [15]. In order to prepare this kind of electrode, the following components are mixed in the ratio 25: 15: 60 parts (graphite: paraffin oil: β-CDs). The constant electrical contact is usually made with a copper wire through the side of the piston. The carbon paste was placed into the holder of the electrode and the electrode was pressed with paper until it had a shiny, smooth surface [16].

2.3.4. Carbon Paste Screen - Printed Electrodes

Miniaturised screen printed electrodes are devices based on varying layers of ink printed on an inert plastic material or ceramic. Simple printing inks were optimised and efficiently applied for the construction of potentiometric sensors [17, 18]. The potentiometric screen-printed electrodes can be prepared as follows: the electrodes are printed using carbon ink containing an appropriate amount of β-CD, potassium tetrakis (4-chlorophenyl) borate (KTPB), o-NPOE (o-nitrophenyl octyl ether), PVC and carbon powder. These electrodes were cured at 320^{o} K for several minutes and dried. The coating of an insulator is then put onto the printed electrodes, leaving a described shape (5 mm × 5 mm) of working surface and a similar area on the other side for the electric junction [19].

2.3.5. Lipophilic Cyclodextrins in Plasticised PVC Membranes

Poly (vinyl chloride) (PVC) based membranes are so far the most commonly used for ISEs (ion-selective electrodes), because of its chemical inertness, high tensile endurance, and good compatibility with the generality active substance in a membrane *e.g.* cyclodextrin. [6]. Especially, α-, β-, and γ-cyclodextrin derivatives of a lipophilic character (with an alkylated hydroxyl group in positions 2, 3, and 6, dihydroxypropyl-β-cyclodextrin, heptakis (2-, 3-,6-tri-O-methyl)-β-cyclodextrin, (2-hydroxypropyl)-γ-cyclodextrin triacetyl-β-cyclodextrin and other CDs, can be applied in plasticised membrane electrodes as remarkable ionophores[20]. These types of electrodes modifiers were also utilised in voltametric and amperometry sensors [21]. In order to prepare a polymer membrane, the components cyclodextrin, PVC, plasticiser and lipophilic salt are mixed and carried on a suitable electrode surface through gelation at room temperature (resulting in THF(tetra hydrofuran) evaporation) [6].

2.3.6. Preparation of Polymeric Films with Cyclodextrins (CDP)

Cyclodextrins are able to create inclusion compounds, when they are in the form of polymers. CDP films can be prepared on an electrode's surface (metal or carbon electrodes) by poly-condensation with dialdehyde electro-condensation following derivatisation [21]. The cyclodextrins can be attached to other poly-

mers, such as chitosan, Nafion, polyaniline,-PANI polyethyleneimine, poly (*N*-acetylaniline) - PAA, polypyrrole-Ppy, poly(*N*-methylpyrrole), poly-3-methylthiophene, through covalent bonds to the monomer, or embedding in the polymer matrix. Cyclodextrin polymeric films can set up a unique medium for the immobilisation of enzymes and redox mediators. They are usually utilised for the construction of amperometry biosensors, where an enzyme is covalently linked to the CDP, while the mediator (*i.e.* 1.4-hydroquinone, 1.4-benzoquinone, ferrocene) is immobilised in the CD cavity and proves charge transfer to and from the enzyme by diffusion. The cyclodextrin polymer films have received successful importance in the last few years, because these kinds of films have good stability, reproducibility, strong adherence to electrode surface, and more active sites [15, 3, 4].

3. CYCLODEXTRINS - A GENERAL CHARACTERISTIC

Cyclodextrins are compounds belong to the macrocycles group, composed of 6, 7 and 8 glucopyranose units. They have an extraordinary ability to form stable complexes through host-guest supramolecular recognition; α-, β- and γ-CDs form a lipophilic inner cavity in the form of a cone. The outer surface of the cyclodextrin molecule has hydrophilic properties. They have a versatile application *i.e.* in the pharmaceutical, food, clothing, cosmetics, and chemical industries [22, 23].

The formation of inclusion compounds made of cyclodextrins and other compounds is possible in gas, liquid, and solid states. These reactions are based on numerous weak intermolecular forces such as: hydrogen bonds, Van der Waals forces, dipole-dipole, and other dispersion forces [24]. The inclusion may also occur as a result of a spatial match between the host and the guest. This is the so-called steric effect which depends on the guest's molecule size, as well as on the presence of functional groups [25]. The driving force behind the formation of inclusion complexes may also be the displacement of polar molecules - for example, the guest molecules present in the solution sample can be replaced by water molecules in a hydrophobic gap, and as a result a more stable state of lower energy is achieved.

The intensity of occurrence of steric effect and the effects related to other intermolecular interactions may depend on particular compounds. Because of the size of the lipophilic cavity, β-cyclodextrins prefers bonds with aromatic and heterocyclic groups, α-cyclodextrins - with aromatic compounds, and γ-cyclodextrins - with steroids and macrocycles.

In the last decade, there have been developments in the electrochemical sensors based on cyclodextrins. Some examples of the most popular cyclodextrins and their derivatives are presented in Fig. (**3**).

CDs are used for the determination of several analytes of organic characters *i.e.* pharmaceuticals, biomedical molecules throughout molecular recognition, formation of inclusion compounds, separation and selective preconcentration of the analyte at the electrode surface [7]. Cyclodextrins can react with other molecules in the solution or in a solid state on the surface of modified electrodes. This review applies on the employ of the complex ability of cyclodextrins in electroanalysis. The potentiometric titrations and cyclic voltammetry can be used to detect the binding constants of inclusion complexes of CDs in solution. Ion-selective electrodes are applied in the study of the equilibrium constant of the inclusion complex formation - K_x. This may be indicative through the measurement of the electromotive force (EMF) in the cells of reference and indicator electrodes and with the use of Hildebrand's equation. The change of the electromotive force with a simultaneous increase of cyclodextrin concentration was caused by the decrease of free ion concentration and formation of the complex. The interpretation of the experimental data used a calculation method which assumes the formation of a complex of suitable stoichiometry [26]. In the current methods, in the presence of cyclodextrins, a decreased anodic/cathodic peak currents and shift in the redox potentials are the results of complex formations due more to the lesser values of the diffusion coefficients of the complexes, than to that of the guest molecule, and to the comparatively high stability of cyclodextrin complexes [8].

4. FABRICATION OF CYCLODEXTRIN BASED NANOCOMPOSITES

4.1. Cyclodextrin with MWCNTs Composites

Remarkable modern nano-materials such as multiwall carbon nanotubes (MWCNT-s) were recently used as an immobilising matrix for electrochemical sensors, including CD. They have favourable properties, good chemical stability, electrical conduction, greater surface area, as well as a relative lack of interaction with chemicals in solution, and wide possibilities of action. They form with β-cyclodextrins or funtionalised CD nano-composite β-CD-MWCNTs which can be assembled on glassy carbon, gold, or indium tin oxide (ITO).

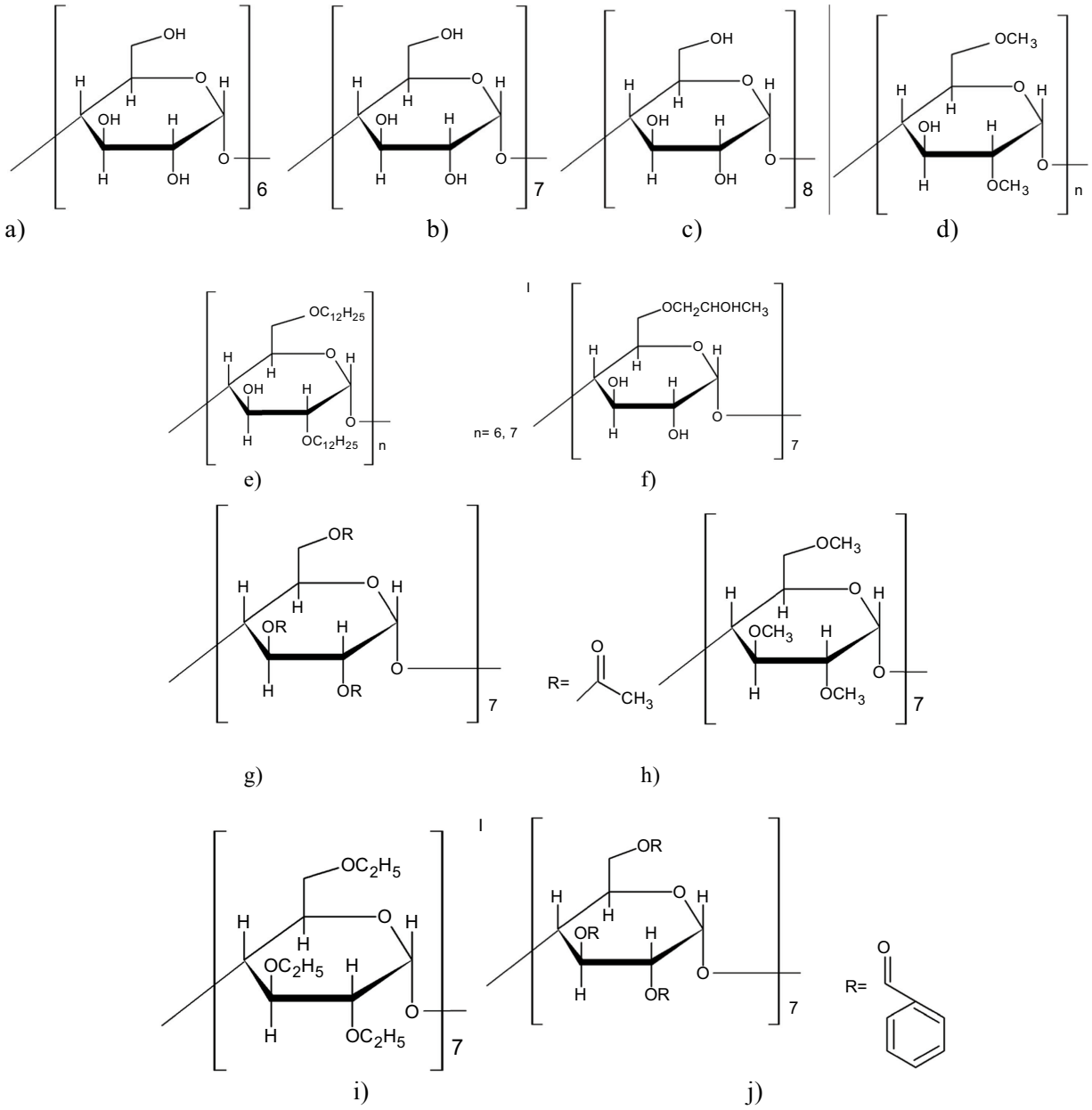

Fig. (3). Scheme of structure selected cyclodextrins and their derivatives: a) α-, b) β- c) γ-cyclodextrins, d) heptakis (2-,6-di-O-methyl)-β-CD, e) 2.6-didodecyl-β-cyclodextrin, 2.6-didodecyl- β -cyclodextrin, f) 2-hydroxypropyl-β-cyclodextrin, g) triacetyl-β-cyclodextrin, h) heptakis (2-,3-,6-tri-O-methyl)-β-CD, i) 2,3,6-tri-O-ethyl-β- cyclodextrin, j) heptakis(2,3,6-tri-O-benzoyl)-β-cyclodextrin.

In order to prepare MWCNT-β-CD composite, it is usually ground, using a mortar and pestle, with an amount of carbon nanotubes with cyclodextrins forming an aggregate, with ethanol added drop-by-drop. After drying, a black product was obtained, which was used to prepare modified electrodes.

A large amount of composites of CDs and MWCNTs such as: CD/MWCNT, CD/MWCNT/ polyaniline, CD/MWCNT/glucose oxidase, CD/MWCNT/ poly (luminol)/AuNPs, and CD/MWCNT/poly (N-acetylaniline [27], have been submitted and entered into the literature.

4.2. Cyclodextrin with Graphene Composites

The use of graphene in sensors and biosensors has been established on graphene-composite or graphene powder modified electrodes. In comparison with carbon nanotubes (CNTs), graphene is a product from graphite which is approachable and cheap. Graphene sheets (GS) are the two-dimensional, carbon substances

and have advantageous properties such as: superior surface area, high conductivity and a wide potential window. Furthermore, they are a biocompatible nanomaterials, and do not contain metallic impurities. Graphene oxide (GO) has been greatly employed in sensors and biosensors as a transducer. It acts as an "electron wire" between the oxidation-reduction centers of the enzyme or protein and the electrode surface, wherein these biomolecules keep their biological activity and constructive integrity when they create mixtures with GO.

Graphene may be also utilised as a conductive assistance for the deposition of electrocatalytic nanoparticles (Pd, Au) creating CD/graphene/NPs films. The other composites of graphene functionalised with cyclodextrins and, also mentioned in the research, are CD/graphene, and poly-CD/graphene/MWCNT [7, 28].

4.3. Nanoparticles Coated with Cyclodextrins

The recent development of gold nanoparticles based biosensors has been performed because of the unique properties of gold nanoparticles. These molecules, on the surface of the electrode, can improve the electron conductivity, which could result in the increase of the peak current [29]. They have the special properties of the immobilisation of biomolecules, keeping their biological activity and effectively conducting interfaces with an electrocatalytic capability [30, 31].

In order to prepare β-CD-GNP nanocomposites, sodium borohydride with CD are dissolved in *N,N*-dimethylformamide and then they are stirred. Then the reaction with $HAuCl_4$ chloroauric acid was carried out in the appropriate time. The obtained nanocomposite product was used for the fabrication of modified electrodes.

Other types of metal nanoparticles, with their biocompatibility, and to the special inclusion capacity of the CD molecules are popular in the application of electrochemical devices. These include: Co, Fe, Zn, Ti, Cu Ag and Au. They are able to be included with cyclodextrins, as they are biocompatible, and so have many applications in biomedical application.

The other parts of this paper which follow concern a review of the literature of electrochemical sensors and biosensors, modified by cyclodextrins. Developed sensors may be used to analyse the compounds of biomedical or pharmaceutical products in samples of a biological origin, such as of the blood, urine or pharmaceutical formulations.

5. REVIEW ON SENSORS IN BIOMEDICAL ANALYSIS

Table **1** Selected surveys of recent electrochemical sensors modified with cyclodextrins for the assay of biological compounds which have importance to human health. The most popular voltametric methods CV, DPV and carbon based electrodes are used. The LDR is usually around 10^{-7}, 10^{-6} M to 10^{-5}, 10^{-4}M.

6. REVIEW ON SENSORS IN PHARMACEUTICAL ANALYSIS

6.1. Potentiometric Sensors

This part discusses the development in the last ten years (from 2006 to 2016) of potentiometric sensors based on selected cyclodextrins or their derivatives and their applications in pharmaceutical research. Especial comments have been paid to the transducer element (the kind of the electric contact between the membrane and the lead-out cable), the composition of membranes (since cyclodextrins are found in various membrane composites *e.g.* PVC, graphite) and some their analytical parameters. The final information concludes on potential application of such electrodes in drug analysis.

Survey of the evidence indicates that the great majority of potentiometric sensors are based on solid contact. Still a small number of electrodes of this group are classic electrodes, Ag/AgCl with a solution of internal electrolyte. The majority of them are solid state electrodes based on graphite, glassy carbon. As ion-sensitive compounds belonging to cyclodextrins, the most frequently used are β-cyclodextrin derivatives, then β-cyclodextrins and the least frequently used are α- and γ-cyclodextrins.

On the basis of the interesting criterion of cyclodextrins, as regards structure and properties recently used as ionophores, there are some authors who use several different cyclodextrins or one type of cyclodextrin. Previous studies from years 2006-2014 describe electrodes in which glucopyranose units' cyclodextrins varied as regards content. The least frequently used are γ-cyclodextrins (several publications), the most frequently used are β-cyclodextrins (21 publications).

Classical Ion-selective electrodes with carbon paste membranes were elaborated through Stefan van Staden, *et. al.* [57-59] for R-baclofen, S-flurbiprofen and vesamicol respectively. In studies of respective electrodes, α-, β-, γ-cyclodextrins as chiral receptors were used successively.The sensitivity of the baclofen electrodes were 59.50 and 51.00 mV/decade for α- and γ-cyclodextrin-based electrodes respectively. The limit of

Table 1. Electrochemical sensors for biomolecules determination.

Analyte	Techniques of Detection	Type of Sensor	LDR (LOD)	Remarks	Refs.
Glucose	Voltammetry, amperometry	GCE modified electrode Au/CMCD/PCMCD	0.001∼110 mM (0.99 μM)	Pharmaceuticals injection sample, 0.1 M NaOH solution	[32]
Cysteine	Potentiometry	CPE electrode polymer membrane with α-, β-, γ-CD, 2-H3-TMAPβCD	10^{-10} - 10^{-3}M	Urine samples	[33]
Adenine, guanine thymine	Voltammetry	GCE modified electrode β-CD/MWNT	4.0 to 20.0μM (0.75 nM) adenine, 80-400μM (6.768 nM) thymine, 100-280 μM (33.67 ± 7.8% nM guanine	Adenine and guanine in DNA of salmon sperm, PBS buffer (pH=7.2)	[34]
Levodopa (L-dopa) Carbidopa (C-dopa)	Voltammetry	CPE (β-CD/PNAANI	0.5-117μM (L-dopa) 1.6-210μM (C-dopa) (0.2 μM (L-dopa)) (0.8μM (C-dopa))	Pharmaceutical formulation, PBS buffer (pH=7.0)	[35]
Guanine, Adenine	Voltammetry	(β-CD-CNT/E	1.0 - 25.0 μM (0.20 and 0.25 μM)	Herring sperm DNA, 0.2 M Acetate buffer (pH=4.5)	[36]
l-phenylalanine	Voltammetry	CPE β-CD-MWCNT/polyaniline imprinted sol-gel film	5.0×10^{-7} to 1.0×10^{-4}M (1.0×10^{-9}M).	Spiked blood plasma samples, PBS buffer	[37]
l-cystine	CV DPVchronoamperometry	GCE rGO/β-CD	1.0-10.0 μM	Model samples, 50 mM sodium acetate and 50 mM phosphate buffer (A-PBS) of pH=7.4	[38]
Dopamine	Potentiometry	Solid-contact polymeric membrane with HMβCD	3.0×10^{-5}-1.0×10^{-3}M (1.3×10^{-5}M)	Pharmaceutical, 2 mMHAc-NaAc buffer solution (pH= 4.4)	[39]
	Potentiometry	Polymer membrane with (β-CD) coated ZNRs gold coated glass	1×10^{-6} - 1×10^{-1} M	Model samples, 10^{-2} M Acetic acid/sodium acetate buffer solution at pH= 5.45	[40]
	Potentiometry	Polymeric membrane with (β-CD) coated Co_3O_4 gold coated glass	10^{-9} - 10^{-2} M (0.06×10^{-6} M)	Model samples of DA solution of concentration 0.1 M with spiked uric acid, urea and ascorbic acid	[41]
	Voltammetry	GC electrode with β-CD-MWNTs) and a polyaniline (PANI) film	1.0×10^{-7}-1.0×10^{-3} M (1.2×10^{-8})M	Pharmaceutical formulation injections, PBS buffer	[42]

(Table 1) contd….

Analyte	Techniques of Detection	Type of Sensor	LDR (LOD)	Remarks	Refs.
	Voltammetry	GC electrode with β-CD-MWNTs and a chitosan multilayer film	5-25 μM	Model samples, 1/15 M, PBS buffer pH= 6.98	[15]
	Voltammetry, DPV	Carbon paste electrode modified with β-cyclodextrin/PNAANI)/CN composite	4-200 μM (down to sub-μM levels (S/N = 3))	Spiked samples of bovine serum, PBS buffer (0.05 M) pH=7.4	[43]
	CV amperometry	GCE electrode modified with MWCNT/β-CD matrix	0.01-0.08 mM (6.7 μM)	Model samples in the presence of AA, pH=7.4	[44]
	Voltammetry, DPV, CV	CPE/poly-β-cyclodextrin electrode	10-130μM (4.1 ± 0.1 μM)	Pharmaceutical samples -injectable solution, pH = 3	[45]
	Amperometry	β-CD-GO/APTMS films on GCE	0.1-800mM (N=3) (7.6 nM) (S/N= 3)	Model samples, PBS buffer pH=7.4	[17]
Cholesterol	Voltammetry, CV, DPV	Grp (graphene) /β-CD/Methylene Blue	0.001-0.10 mM	Model samples, PBS buffer pH=7.4	[46]
Uric acid	Voltammetry, CV, amperometry	CPE/β-CD	1×10^{-5} - 1×10^{-4}M ($4.6\pm0.01\times10^{-6}$M (S/N=3)	Urine, saliva samples in the presence of AA, acetate buffer pH=5.0	[47]
Butyrylcholinesterase	Potentiometry	Screen-printed, based on carbon modified with β-cyclodextrins:	10^{-5} - 10^{-2} M (8×10^{-7} M)	Commercial pesticide samples, human serum, PBS buffer pH=7.3	[24]
Phospholipid	Voltametric, CV	ITO electrode modified ofβ-cyclodextrin in silicasol-gelfilms	1-100mM	Model samples, in 0.1 M Bu_4NClO_4	[48]
Catechin	Voltammetry, OSWAV, DPCV, CV	CPE modified HP-β-CD	7.20- 4.20 μg/mL[1] (0.12and 0.30 ng/mL)	Urine samples pH=4.40 in 0.10 M BR buffer	[49]
Iso-orientin	Voltammetry, CV, DPV	CPE β-CD/K_{10} Mt	2.5×10^{-7}- 2.5×10^{-5} M (2.95×10^{-7} M)	Model samples in the presence of AA, 0.10 M BR buffer	[50]
Creatinine	Voltammetry, CV, potentiometry	GCE modified PEDOT/βCD	10^{-4} - 10^{-1}M(potentiometry)	Model samples,0.1 M Tris-buffer	[51]
DNA	Voltammetry, CV, DPV	CD/PNAANI/CNT/ SPE	0.01 - 1.02 mM (5.0μM)	Model samples 0.1M PBS buffer pH=7.4	[52]
Tyrosine, guanine, adenine, thymine	Voltammetry, CV, DPV	GC, Au or ITO modified, functionalised MWCNTs with HPβCD	0.3-1.8 (0.66 mM) 3.6-13.2 (0.09mM) 0.6-3.0 (7.78mM) 1.2-7.2 (3.50mM)	Model samples 0.1 M PBS buffer pH=7.4	[53]

(Table 1) contd….

Analyte	Techniques of Detection	Type of Sensor	LDR (LOD)	Remarks	Refs.
DNA	DPV	β-CD/ PNAANI/GCE and m-toluic acid(mTA)-labelled probe DNA (mTA-DNA); Methylene blue (MB) and daunomycin (DNM)-as two intercalators that electrochemical indicators were used	1×10^{-12}- 1×10^{-9} M (7.6×10^{-13} M) for MB 1×10^{-12}- 1×10 M (6.0×10^{-13}M) for DNP	0.01 M PBS	[54]
Guanine, adenine	DPV, CV	AgNPs-β-CD-Gr/GCE	0.3-200 (0.09 μM) 0.5-250 μM (1.15 μM)	Denatured herring sperm DNA, buffer solution (pH=3.7)	[55]
DNA	CV	DNA/TCT/CD-Gr/ GCE	1.0×10^{-16}- 1.0×10^{-12}M (3.4×10^{-17} M)	Hybridisation with various DNA sequences	[56]

detection was better for γ-cyclodextrin-based electrodes and close to the value of 1.44 x 10^{-10}mol L^{-1}. The flurbiprofen sensors showed very low limit of detection (of 10^{-8}-10^{-9}mol L^{-1}), comparable slope of characteristic of 56.1 - 59.9 mV $decade^{-1}$ in the concentration range of 1.5×10^{-3} - 1.5×10^{-8}mol L^{-1}. The best Nernstian response was obtained for a β-cyclodextrin based electrode. A range of linearity for the vesamicol sensors achieve the values from 10^{-9} to 10^{-7}mol L^{-1} for electrodes with α-, β- cyclodextrins with limit of detection of 5.7×10^{-10}, 2.42×10^{-10} mol L^{-1}, respectively. Relatively less favourable parameters were obtained by electrodes with γ -cyclodextrin. The electrodes displayed near-theoretic slopes of 52-59 mV $decade^{-1}$of l-vesamicol concentration. The working period of the constructed electrodes [57] was six months. The proposed electrodes can be employed for the determination of R-baclofen, S-flurbiprofen, vesamicol in pharmaceutical formulation Norton-Baclofen® tablets, Froben tablets and serum samples. The average percentage recovery for *R*-baclofen was 2.65 ± 0.09% and 2.89 ± 0.06% for α- and γ -cyclodextrin sensors respectively. Determination by using flurbiprofen can yield 99.90% ± 0.2% RSD of the active substance.

Further studies, in which all three types of α-, β- and γ-cyclodextrins were studied, are studies of electrodes for midazolam, diazepam [60] acetylcholine (ACh) derivatives [61], promethazine [62], sulfadiazine (SDZ) [63] and piroxicam [64]. For midazolam and diazepam solid contact electrodes [60] with 2-fluorophenyl 2-nitrophenyl ether as a plasticiser, PVC-COOH and potassium tetrakis (p-chlorophenyl) borate as an ionic additive, good, analytical parameters were obtained. Near Nernstian slope of characteristic of 61.9 ± 1.3 mV $decade^{-1}$, a lower limit of linear response LLLR of 5.7 ± 2.7×10^{-4} g L^{-1} and pH range of 2.6-5.4 (for midazolam) and slope of characteristic of 67.6 ± 3.0 mV $decade^{-1}$, LLLR $4.9\pm1.5\times10^{-2}$ g L^{-1} and 1.9-2.7 pH units, respectively, for diazepam respectively. These parameters were achieved for electrodes with optimal ionophore, that is β-CD with the lipophilic additive (1:4 ratio) for midazolam, and 2-hydroxypropyl)-γ-cyclodextrin for diazepam. Diazepam electrodes containing α-CD and β-CD respectively, obtained reproducible super-Nernstian slope of characteristic. Electrodes with α-CD, obtained a higher limit of detection. The miniaturisation of potentiometric electrodes gives rise to detectors for sequential-injection lab-on-valve (LOV) flow system. The optimised flow cases were obtained for sample injection volumes of 20 μL with a flow rate of 16 μL s^{-1}over 80s. The drugs in pharmaceutical samples were determined with the use of injection analysis and the results were satisfactory: recovery 97-104% for diazepam, and 100.7% for midazolam.

The authors of the study [61] prepared electrodes sensitive to acetylcholines and their derivatives, which include: butylcholine (BCh), acetylmethylcholine (AmCh) and acetylthiocholine (AtCh). It was concluded that only β-cyclodextrins and their derivatives demonstrate the abilities to form inclusive compounds, while the remaining cyclodextrins do not have compatible cavities to form such complexes. Type of electrode: PVC, CPE, The better parameters were shown by PVC electrodes than CPE (carbon paste electrode).

The selected optimal electrodes sensitive to acetylcholine satisfactorily showed the concentration range from 10^{-6} to 10^{-2} mol L^{-1}detection limit 8.3×10-7 mol L^{-1} attained and a fast response time of 2s. The constructed electrodes have a stable theoretic slope of characteristic in the working pH range 3-10. The selectivity coefficients for acetylcholine derivatives towards various ions K^+, Li^+, NH_4^+, (-log K ~3.8) and molecules: choline citrate, starch glycine (-log K ~2.5), caffeine (-log K ~2.5) maltose (-log K ~2.4) sucrose (-log K ~2.0) were determined. The sensors were efficiently applied in the electrochemical determination of acetylcholines and its derivatives under two conditions: potentiometric titration and flow injection analysis (FIA).

Plasticised with bis (2-ethylhexyl), adipate PVC-based membranes were estimated for their potentiometric behaviour towards **promethazine** (PM) under flow injection analysis (FIA) [62]. The best characteristics were achieved when β- CDs with tetrakis (4-chlorophenyl) borate (KTPB) were used. The linear concentration range was from 1×0^{-5} to 1×10^{-2}mol L^{-1}, sensitivity was 61.3 mV $decade^{-1}$, the pH range amounted to 4.5 - 7.0, and a limit of detection of 5.3×10^{-6}mol L^{-1} was practicable. The sensor was investigated under flow injection analysis and was also examined to the quantitative determination of promethazine in pharmaceuticals and human urine samples, with mean recoveries for spiked urine samples of 98.6%.

The electrodes for the sensitive determination of sulfadiazine **(**SDZ) used an epoxy-graphite matrix as a solid contact [63]. The membranes were made from PVC doped with α-, β- and γ-cyclodextrin with tetraoctylammonium bromide, which were dissolved in NPOE as a solubiliser. The electrode with β-cyclodextrin showed a theoretical slope of characteristic, regardless of the amount of the lipophilic additive. The electrodes can work independently, in the sulfadizine solution of pH 2-7. All of them have a very short response time - about 15s. The proper time of sensor functioning, stored in 10^{-3} M with reproducible slope of the curve in the range ±3%, amounts to two months. The method exhibited the advantages of accuracy, simplicity, precision (recoveries ranged 93.6 - 102.9%) and automation of practicability.

The novelty in the work [64] was the employment of the new potentiometric electrode for piroxicam, not yet discussed in scientific literature. This carbon paste electrode contains functionalised multi-wallet carbon nanotubes (MWCNTP-CPE) in the membrane cocktail. The modification included oxidation of the carbon nanotubes in the acidic environment (groups -COOH were incorporated). Then, the tubes were triturated with alcohol and β-cyclodextrin. The optimisation and the selection of the best piroxicam electrode consisted, in the comparison of analytical parameters of the electrodes of three different matrix compositions and achieving relevant, of most important conclusions and findings: the carbon paste electrodes (MWCNTP-CPE), containing multi-wallet nanotubes in the graphite matrix, enlarged the surface of the electrode, and their aim was to capture ions on the paste surface. Electrodes of this type improved the parameters and they achieved a broader linear range 1×10^{-6} - 1×10^{-2}mol L^{-1} and a lower LOD $1.0x10^{-6}$ M, and also a lower slope of the characteristic -51.1 mV $decade^{-1}$ The other sensors based on functionalised FMWCNTs/β-CD-CPE) replaced free cyclodextrin placed on the graphite paste, and hyamine (Hy). Such electrodes have shown optimal parameters, achieving the range of linearity 10^{-6} to 10^{-2}mol L^{-1} with Nernstian performance (58.7±0.9 mV $decade^{-1}$) with the fast response time of about 2s, and provide an adequate operational life-time (4 months).The proposed electrodes have been used for the quantitative determination of piroxicam in drugs formulation under batch and flow injection analysis. FIA allows for the analysis of 120 samples h^{-1} with the accuracy, automation and of simplicity.

The three electrodes with a polymer membrane containing α-cyclodextrins were prepared for the determination of amantadine [65], atropine [66] and ibuprofen [67]. For preparation of the membranes, other plasticisers were used such as: dibutyl phthalate, [65], o-nitrophenyl-octylether [66, 67], 2-fluoro-nitrodiphenyl ether [65, 67] with ion exchangers such as: potassium tetrakis [3.5-bis- (trifluoromethyl) phenyl] borate (KTFPB) [65], phosphotungstate [66], ammonium bromide [67]. These achieved electrodes are characterised by stable responses with a life-time of over a year [65], near Nernstian, fast, stable response of 51 mV $decade^{-1}$for 1×10^{-2} to 1×10^{-6}mol $L^{-1}$of atropine, the pH range 3-8 and the response time 20-45s [66], For the ibuprofen electrode, the Nernstian sensitivity of -59.0 mV per decade in the concentration linear range 3.87×10^{-6} to 10^{-2}mol L^{-1}, for samples with a pH adjusted to 9, was achieved. The response time was 15s and the potential was reproducible (±0.8 mV), with a constant efficiency during about 6 months. The practical LOD was of (3.34×10^{-6}mol L^{-1}).

The amantadine electrode can also be applicable for the determination of the active ingredient in pharmaceuticals (in Parkadina 100 mg per capsule), with a very good precision (RSD < 2.9%) and a yield of

108%. The urine samples with amantadine addition give the results of determination of 96.7% recovery and RSD (0.5%). The direct determination of atropine in eye drops and injections offers a mean relative standard deviation (RSD) of 1.6%, with an average recovery of 98.6% at 100g/mL. The analytical usefulness of the ibuprofen electrode was examined by determining the active substance in pharmaceuticals with variation coefficients of less than 1%

The complex properties of β-cyclodextrins were used to develop electrodes sensitive to tobramycin [68], hyoscine butylbromide [69], cetrizine [70], amantadine [71], thiamine and pydidoxine [72], tetracycline [73], metronidazol and spiramycin [74], sitagliptin [75], oxicams [76], neostigmine [77]. In another study [78], a clarithromycin electrode was used to determine the coefficient of complexity of clarithromycin with β-cyclodextrin.

Modified with β-cyclodextrins, electrodes for the determination of the aforementioned drugs have a varying transducer element. The following ought to be mentioned: classical electrodes with inner solution [68, 69, 70] carbon paste electrodes [70, 71, 77, 78], graphite /epoxy resin support [72, 73], micro-size graphite [74], screen printed electrodes based FMWCNT [76]. The majority of electrodes had polimer membranes containing polar NPOE, 2-fluoro-2nitrodiphenyl ether, lipophilic di butyl phthalate, dioctyl phthalate and ionic additives *e.g.* tetrakis fluoroborate [68], ammonium Reinckeate [69], potassium tetrakis [3-, 5-bis (trifluoromethyl) phenyl]borate (KTFPB) [70], potassium tetrakis (p-chlorophenyl) borate [72]. The electrodes display favourable analytical parameters, theoretical calibration surve coefficient [70, 74, 75, 76, 77], or slightly lower or higher for the other electrodes in the linear range of 10^{-7} - 10^{-2} mol L^{-1} [76, 77], 10^{-8} - 10^{-2} mol L^{-1} [75], 10^{-6} - 10^{-2} mol L^{-1} [69,70], 10^{-5} - 10^{-2} mol L^{-1}[68,73].

These electrodes were applicable for determination of an active substance in the pharmaceutical and biological samples. The tobramycin electrode was efficiently applied to the determination of tobramycin recovery, "by 100 µl *E. coli* suspensions in the presence of up to 10 µg ml^{-1} of EDTA solution, with average recovery of 99.3 ± 2.77%".

The cetirizine electrodes were used to assay cetrizine in pharmaceuticals and in spiked human urine. The results show recoveries in pure samples and pharmaceuticals of 99.5±0.4 and 99.8±0.3% for conventional electrode and carbon paste electrode. The quantification of cetrizine in biological samples was conducted by the use of standard addition method; the recoveries obtained were 100.9, 99.0% for ISE and CPE electrodes respectively. The mean standard deviation was SD ± 0.4.

Amantadine was assayed in its pharmaceutical preparations with an accuracy of 2% in a blood-serum sample with a recovery of 94% from the sample of concentration 2.5×10^{-8}mol $L^{-1.}$

Metronidazol and Spiramycin were determined with the yield percentages of 99.86 ± 0.249% and 99.69 ± 0.856% respectively.

The sitagliptin sensor demonstrated a very useful analytical utility for the recovery studies in different pharmaceutical forms, and biological fluids (urine, plasma). After the addition of 10^{-6}(0.539) µg/ml of the drug, it was found in100.33±0.91 (in plasma) and 10^{-7} (0.0539) µg/ml of the drug - and100.28±0.98 (in human urine) was achieved.

The constructed electrodes provide the excellent advantage of sitagliptin determination in biological fluids without pretreatment steps, which is comfortable for controlling STG concentration in clinical studies.

The oxicam sensors provide a non- complicated analytical tool for different oxicam derivatives analyses in their other pharmaceutical forms (Zeficam, Moxen, Tenoxil, Dispercam) under batch (98.5-100.2% , RSD 1.2 -2.0%) and flow injection analysis (FIA) conditions (98.1 - 101.5%, RSD 1.0 -1.9%).

Other two studies [79, 80] compared complexing properties of β-cyclodextrin and β-cyclodextrin derivatives in constructions of electrodes sensitive to vitamin B1 and vitamin B6 [79], and dextromethorphan [80].

The first sensor [79], for vitamin B1, contained 0.04g of the active substance (2-hydroxypropyl-β-cyclodextrin), 0.4g of mediator solvent (FNDPE) and 0.18g PVC-COOH. The sensors for vitamin B6 contained in the membrane β-cyclodextrin (sensor 2) or more lipophilic 2-hydroxypropyl -β-cyclodextrin (sensor 3), dissolved in components of the same quality and quantity as the components of the membrane. The most important conclusions concerning the characteristics of the study include: electrodes sensitive to vitamin B6 do not show any considerable differences as far as the parameters are concerned. Near Nernstian slopes of 60.6 ± 0.6 and 61.1 ± 1.4 mV $decade^{-1}$, within the intervals of 5.8×10^{-5} to 1.0×10^{-1} and 4.3×10^{-5} to 1.0×10^{-1}mol L^{-1} were obtained, for thiamine and pyridoxine I and II prepared electrodes, respectively.

Analytical determination of vitamins B1 and B6 in complex multivitamin drugs was acquired with yields within the intervals of 95.1-99.6% for vitamin B1 and 95.1-102%for vitamin B6.

The silver coated wire electrode (CWE), coated graphite electrode (CGE) and the conventional PVC membrane electrodes (CE) for sensitive determination of dextromethorphan (DXM) were described [80]. The quantitative composition of the analysed membranes was as follows: ionophores β-CDs derivatives including; heptakis (2-, di-o-methyl)-β-CD heptakis (2- , 3- , 6-tri-o-methyl)-β-CD, 2-hydroxypropyl-β-CD and native β-CD, lipophilic additive and (PVC).

The preliminary research concerning the selection of the best group of cyclodextrins allowed for the drawing of a conclusion that the most compatible group of these macrocyclic particles for determining dextromethorphan are β-cyclodextrins. It is assumed that they form inclusive compounds with the analysed drug in the 1:1 ratio. Lipophilic cavity incorporates methoxy groups and the part of the adjoining aromatic ring of dextromethorphan.

The new developed sensors have been efficiently applied for the determination of DXM in pharmaceutical preparations under two conditions: batch and flow injection analysis. FIA receive the analysis of 90 samples h^{-1}, the average peak heights of which were 187 ± 2.0 mV.

The potentiometric titration was conducted with the use of titrant tetraphenylborate sodium. A potential jump between 274 and 380 mV was noted in ideal conditions (when the two curves are symmetrical), determining 0.8 mg of dextromethorphan. The proposed sensors offer the advantage of accuracy, simplicity, and automation practicability.

Among β-cyclodextrin derivatives used as modifiers of potentiometric sensors, the most frequently used in recent years is 2-hydroxypropyl β -cyclodextrin (HPβCD) [81-95]. This cyclodextrin was used as a complex component for the construction of the following electrodes sensitive to: pyridostigmine bromide [81].

Amlodipine besilate (AM) [82], cyclobenzaprine hydrochloride [83], neostigmine bromide [84], hydrochloride (MEM) and pramipexoledihydrochloride monohydrate (PXL) [85], pramoxine [86], amilsupride [87], metoprolol tartrate (MT) and Hydrochlorothiazide (HZ) [88], rivastigmine (RIV). [89], ambroxol [90], trigonelline [91], itopride hydrochloride [92], fluconazole [93], naloxone hydrochloride [94], nicotinamide [95].

The membranes of the electrodes were based on PVC plasticised with NPOE [84, 86], DBS [87], DOP [92],DBP [93] or modified with COOH groups of polyvinyl chloride plasticised with NPOE [81, 91], DBS [82, 83, 85] or DOP [88, 94].

The studied electrodes display good working parameters and analytical usefulness, as shown below.

Pyridostigmine bromie [81] sensor achieved a linear range of 10^{-5}-10^{-2}mol L^{-1}, with slopes of 56.7 ± 0.40 mV/decade over a pH range of 5-10, which was acquired.The proposed sensor was applied for assay of PB with an average yield of 100.22 ± 0.62, and in 99.14 ± 1.19 in pharmaceuticals and plasma samples respectively.

Amlodipine besilate [82] shows a linear range of calibration graph of 1×10^{-5}-$1\times10^{-3}$with a slope of 26.8 ± 0.45% mV $decade^{-1}$ in a pH range of 3-6 and a low limit of detection of 7.5 x 10^{-6}mol L^{-1}. The yield percentage for the determination of amlodipine in the synthetic samples was 99.78 ±0.382%, in pharmaceuticals 99.12 ± 0.44% and 100.54 ± 0.49% in plasma samples of the concentration 10^{-3} and 10^{-4} mol L^{-1} respectively.

Cyclobenzaprine hydrochloride [83] can work properly with slopes of 55.5 mV $decade^{-1}$ in the linear concentration range of 1×10^{-4} - 1×10^{-2}mol L^{-1}, over a pH range 2-4. The representative sensor showed useful analytical properties for determination of CZ in synthetic samples form, with average recoveries 99.61 ± 0.34% and in plasma samples with good recoveries.

Neostigmine bromide [84] the concentration ranges of 10^{-6} to 10^{-2}mol L^{-1}, slope of 52.9 ± 0.6 mV $decade^{-1}$ over a pH range of 4-9 were achieved.

Amisulpride[87] this electrode has the highest sensitivity of 31.1 mV per $decade^{-}$ over the linear concentration range of 1×10^{-6} - 1×10^{-2}mol L^{-1}, a response time of 10-20s and the dependence of a potential of pH 4.0-7.0 in the period of 4-6 months. The sensors were evaluated for the determination of amisulpride, in synthetic samples, tablets, plasma, and in the presence of its degradation products, gave average recoveries 99.94±0.87.

Rivastigmine (RIV) electrode [89] shows that a linear concentration range of 10^{-6} to 10^{-2}mol $L^{-1}$with slope characteristic of 54.6 ± 0.7 mV per decade was obtained. The potential is practically independent between pH 4.0 and 7.0. The obtained sensor was applied for the determination of RIV in pharmaceutical formu-

lations and do not require preliminary steps of sample preparation (the recovery was 99.53±0.707). The acquired sensor proved a useful analytical application for the analysis of RIV in biological fluids and in the presence of its degradation product and therefore may be used for stability-indicating assays.

Ambroxol [90] PVC conventional polymeric membrane and carbon paste type sensors show Nernstian responses of 56.29 ± 0.3, and 58.32 ± 0.2 mV per decade, respectively, at standard conditions between concentration ranges of 1.0×10^{-6} - 1.0×10^{-1}, and 1.0×10^{-8}-1.0×10^{-2}mol $L^{-}1$. The ambroxol in pharmaceutical samples and biological fluids was determined with satisfactory validated results by the standard addition method comparable with other previous reported methods.

Trigonelline [91] proposed sensors successfully showed slopes of 59 mV per decade in the linear range over pH from 4.0 to 9.0, and the concentration range covered 10^{-3} - 10^{-5}mol L^{-1}. A very short response time of 15s, and 5-week stability for the electrode were obtained. The selectivity of the elaborated trigonelline sensors showed excellent values towards: Isoleucine, Leucine, Lysine, Vitamin B2, Vitamin B3, K^{+}, Na^{+}, Zn^{+2}, Mg^{+2}, (K = 1- $6x10^{-3}$). The exhibit electrode was favourably applied for direct analysis of trigonelline in Trigonellafoenum-graecumseeds extract without prior purification or pre-treatment steps, and in plasma. Medium yield and medium standard deviation in the plasma samples were ± SD 100.06 ± 0.55 99.82 ± 1.10 (n=3).

Naloxone hydrochloride (NLX) [94] the presented sensor shows a constant sensitivity of 57.0±0.5 and 58.1±0.2 mV per decade (for the other) in the concentration range1.0×10^{-7}-1.0×10^{-2} and 1.0×10^{-8}-1.0×10^{-2}mol L^{-1} respectively. The elaborated method was validated and show satisfactory results for quantification of NLX in its pharmaceutical formulation and biological fluids.

Nicotinamide [95] this electrode has shown a slope of 54.6 ± 0.8mV $decade^{-1}$over drug linear range of 5.0×10^{-7} - 5.0×10^{-2}mol $L^{-1.}$ The fabricated sensors were used for the determination of nicotinamide in bulk drugs, pharmaceuticals and biological fluids. Statistical treatment was applied to analyse the obtained results and the calculated data were similar to those achieved from other previously published techniques.

The other ion selective electrodes sensitive for R-clenbuterol [96], metformin [97], ephedrine [98], diclofenac [25], risperidone [99] and naproxen [100] contain other β-cyclodextrins as modifiers of polymer membranes.These are cyclodextrins in the chloride form [96, 100], methyl derivatives [25, 97, 99, 100], a benzyl derivative[100], and a triacetyl derivative [98].

For **R-clenbuterol** [96] carbon paste sensor, 2-hydroxy-3-trimethylammoniopropyl-β-cyclodextrin (in the form of chloride salt) was applied. The range of linearity was between 10^{-6} and 10^{-3}mol/Land a limit of detection of $2.99x10^{-7}$ mol L^{-1}. The EMF is not dependent on the pH in the pH range 5.0-9.0. Potentiometric selectivity coefficients for the enantioselective electrode for R-Clen are, respectively: for S-Clenbuterol $4.2x10^{-3}$, Creatine $4.0x10^{-3}$, Creatinine $8.0x10^{-3}$ PVP $8.0x10^{-3}$. R-clenbuterol was yielded from synthetic samples as well as from serum samples in a phosphate buffer of pH 6.4 with average recoveries higher than 99.10%.

The **metformin (Mf)** [97] miniaturised CWEs and CGE electrodes were prepared, based on heptakis (2.6-di-o-methyl)-β-CD heptakis (2-, 3-, 6-tri-o-methyl)-β-CD, 2-hydroxypropyl-β-CD and native β-CD. It was also established that the degree of inclusion (complexation constant) with the examined drug increased according to the following sequence: heptakis (2-, 3-, 6-tri-o-methyl)-β-CD >heptakis (2-, 6-di-o-methyl)-β-CD> 2-hydroxypropyl-β-CD and native β-CD. Methylated cyclodextrins became more lipophilic, and hence provided better penetration of the lipophilic particle of the drug inside the inclusion cavity in comparison with natural hydroxycyclodextrin (inert, with no substituents). Moreover, the presence of hydroxypropyl substituents in 2-hydroxypropyl-β-CD, hindered the formation of the complex with the guest's molecule .Therefore, CWEs modified, with HMβCD, NaTFPB as lipophilic salt and 2-fluorophenyl 2-nitrophenyl ether (f-NPE), works acceptably. The electrode was utilised for the determination of Mf under two condition batches and FIA. FIA allowed for the determination of 90 samples per hour with accuracy, simplicity and automation feasibility. The dissolution range for the drug metformin (Cidophage®) was controlled with the use of the described electrode.

The advantages of **ephedrine** electrodes [98] with membrane phase of the following composition: 32.7 % wt. PVC, 1.0 % wt. of triacetyl-β-CD, 65.8 % wt. DOS, and 0.5% TPB^{-} are near Nernstian slope of the characteristic 57.0±0.3 in the range 3.0×10^{-5} - 8.0×10^{-3}mol L^{-1} and low detection limits of 5.7×10^{-6}mol L^{-1}. The working pH range is 3.0-8.0 and the response time is 10-20s. The developed sensor for ephedrine is characterised by a long lifetime - 5 weeks, with good selectivity for EP

Dover a wide variety of other species, high reproducibility, long-term stability, acceptable accuracy (99.5%) and precision (CV=0.4%).

The **diclofenac** [25] electrode, without an inner solution with a PVC membrane, contains two layers: the inner layer containing plasticised PVC in which the Ag/AgCl electrode is placed. The outer layer consists of: PVC, plasticisers and an appropriate amount of cyclodextrin, with tetraoctylammonium chloride.

The optimal performance of the diclofenac electrode was obtained for selected sensors with HSM βCD+DIBP, HSMβCD+o-NPOE, HSBβCD+o-NPOE, HPβCD+o-NPOE respectively.

The overall good characteristics, including a wide concentration range 5.0×10^{-5}-1×10^{-2}mol L^{-1}, a low limit of detection (1.0×10^{-5}-5.0×10^{-5}mol L^{-1}), and a reproducible theoretic slope, were obtained.

The electrical properties of the membrane electrode were researched by impedance spectroscopy. For the studied electrode, bulk resistance was 945 kΩ and geometric capacitance was 39.3 pF. The considerable advantages of the diclofenac-selective are that the electrode contains high sensitivity, selectivity, cost-effectiveness, and convenient application in pharmaceutical and urine samples analysis. The percentage yield from six replicate diclofenac measurements was found to be 94.0-100.5% (RSD 2.2-3.4%) for synthetic solutions, 96.1-98.8% (RSD 2.5-4.5%) for pharmaceutical samples and 99.0-99.7% (RSD 2.7-3.1%) for urine samples.

Solid contact sensors risperidone [99] achieved a linear range from 5×10^{-6} to 10^{-2}mol L^{-1} with a sensitivity of 59.9±0.7 mV $decade^{-1}$ and a limit of detection of 2.7×10^{-6}mol L^{-1}.

The sensor was applied for the potentiometric analysis of RIS in the drugs: Sigmdone (3 mg/tablet) and Psychodal (1 mg/tablet) under batch experiments for Sigmdone (97.3±0.08) and flow injection analysis (FIA) (103±0.05).

The novel **naproxen** electrode, based on neutral β-cyclodextrins: HPβCD, HMβCD, HBβCD, and anionic 2-H3-TMAPβCD are proposed [100] (Fig. **4**). The IR spectroscopy method was applied for the study of inclusion complexes of naproxen with the presented cyclodextrins. These electrodes were described in detail in terms of the composition of the polymer membrane, calibration curves, pH range, and response time. A theoretic slope of 59.0 ± 0.5 mV per decade between the concentration of $5.0\times10^{-5}$to 1.0×10^{-2}mol L^{-1} and the detection limit 1.0×10^{-5}mol L^{-1}) for an electrode based on HBβCDare was achieved. Incorporation of β-cyclodextrins improved the electrode's selectivity compared with earlier naproxen electrodes, due to non-covalent bonds (host molecule-guest molecule). The considerable advantages of the naproxen-sensor include its cost-effectiveness, as well as an accurate and comfortable application in pharmaceutical analysis (an accuracy of 1.7-3.3% and RSD 1.2 - 2.6% in pharmaceutical preparations).

6.2. Voltametric and Amperometry

Voltametric and amperometry sensors, have, in the recent decade, become an intensively growing group in the department of pharmaceutical analysis. They are suited for the analysis of drugs because of the development of relatively simple matrixes with one electrochemically active compound present, with other, usually inactive substances, present. In this section attention has been paid to the structure of the electrode and the transducer element, their selected analytical parameters and the possibilities of their applications.

Recently the electrochemical sensors based on glassy carbon, or bare metal (gold) are the most popular. The scheme of preparing of such these sensors are presented in Figs. (**5** and **6**).

6.2.1. Methotrexate (Mtx)

Carbon paste electrodes, modified with hydroxypropyl-β-cyclodextrinhave, been investigated for the enantioselective voltametric determination of methotrexate [101]. The immobilisation of the HPβCD (9% w/w) on the surface of the electrode, significantly contributed to an increase in the oxidation peak current. By using square-wave anodic stripping voltammetry, the optimal resolution of enantiomers (R = 2.96) was obtained at pH=6.4 in the PBS buffer, in the accumulation time of 60s. The received distribution is sufficient to estimate the main compound-distomer d-Mtx at 0.1% (m/m of l-Mtx).The interference of $Cl^{-}SO_4^{2-}$, $NO_3^{-}$and metal ions like $Na^{+,}$ K^{+}, Ca^{2+}, Zn^{2+}, Fe^{2+}, Fe^{3+}, and Cl^{-}, and organic compounds such as gelatin and other surface-active compounds (*e.g.* SDS, CTAB and TritonX-100) in the peak current response was investigated. This voltametric sensor can be successfully applied to determine simultaneously ssDNA (Single Stranded Calf thymus DNA) reactions with l-Mtx and d-Mtx. As a result, the stability of d-Mtx-ssDNA diastereomeric complexation is superior to that of l-Mtx-ssDNA, which can be used in medicinal chemistry to test many phenomena applied with the carcinogenic

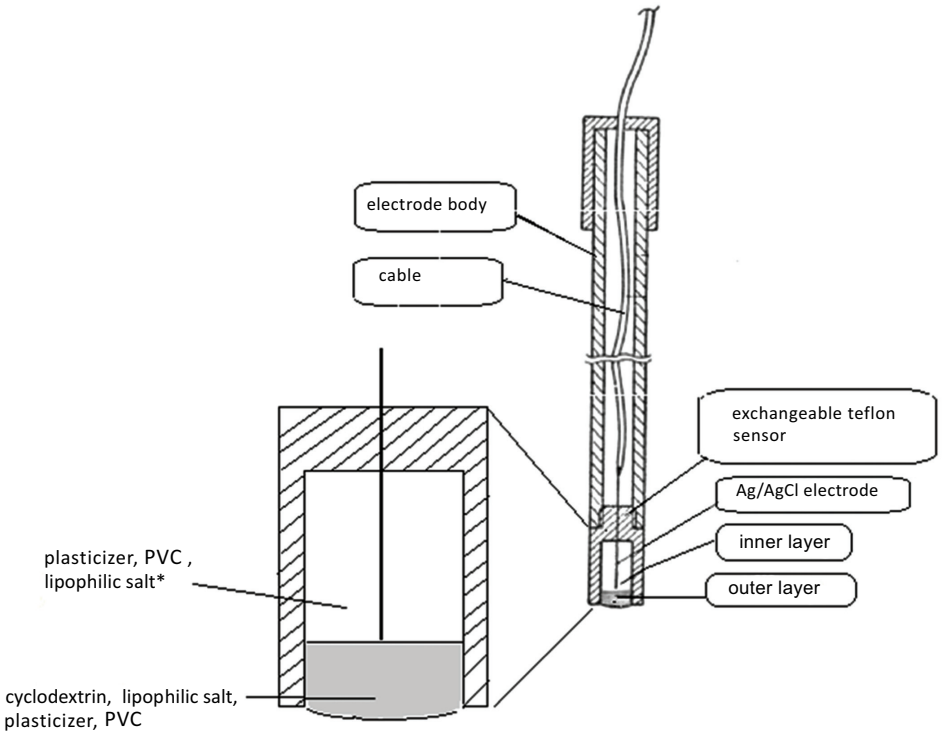

Fig. (4). A scheme of a PVC two-layer membrane phase of polymer potentiometric sensor electrode [100].

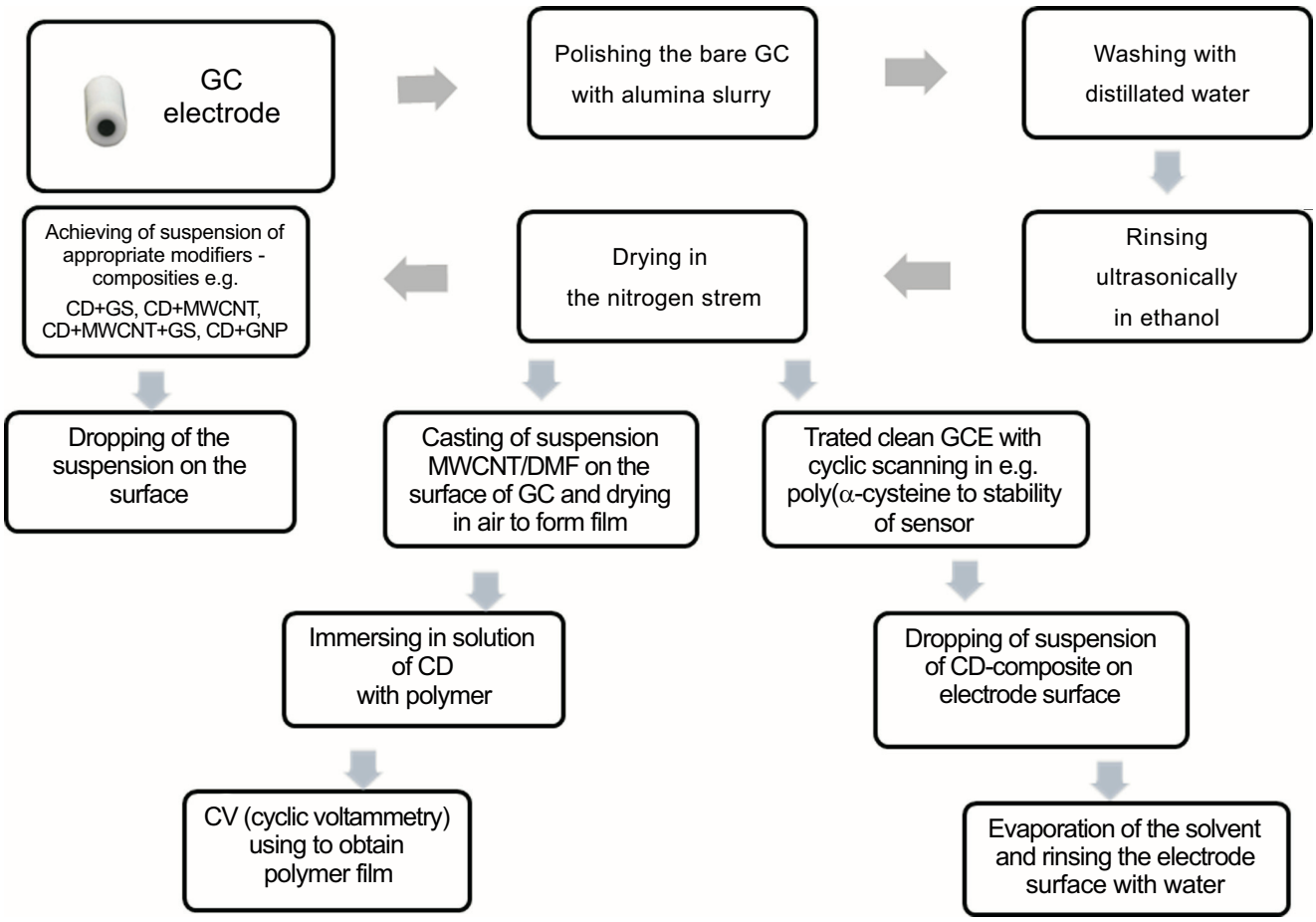

Fig. (5). A scheme for the preparing of glassy carbon modified electrodes.

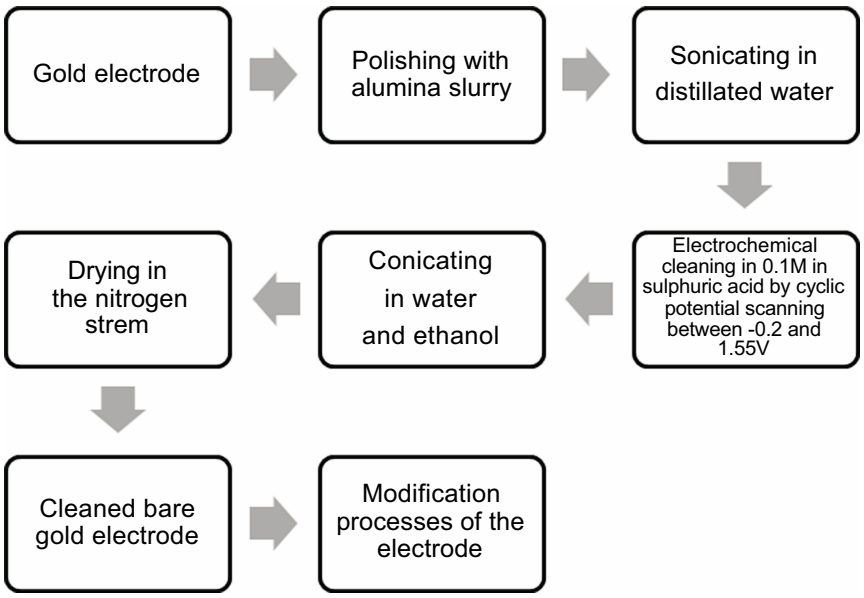

Fig. (6). Scheme for the preparing of metal based electrodes.

effect of MTX. Adsorptive stripping voltammetry is employed to the determination of main therapeutic drug- l-Mtx and d-Mtx (distomer) in commercial pharmaceutical formulations. The percentage yields of l-Mtx and d-Mtx assay have been included between 99.85%-101.60% and 99.50%-101.20% in injections and tablets, respectively with a standard deviation of about 6.00%.

6.2.2. Fluoroquinolones

Electrochemical sensors for ofloxacin (OF), norfloxacin (NF), gatifloxacin (GF), and lomefloxacin (LF) were prepared [21]. With CPE modified with β-cyclodextrin. Both the voltametric techniques CV and DPV were applied for the deposition of drugs (at a concentration of 2×10^{-5} M in a BR buffer solution at pH=4.0) on the electrode's surface. Preconcentration at CDMCPE was made possible by the complexation between the quinolone group of drugs and β-CDs. The scan rates on the peak currents of NF, OF, GF, and LF were proved to increase linearly with increasing scan rates from 80 to 150 mV/s, proposing that the reaction is an adsorption-controlled process. The accumulation potential of -0.5 V at pH=4.0 was proved. The optimal preconcentration time at 2.0×10^{-5}mol $L^{-1}$of fluoroquinolone took 160s. The cathodic current was proportional to the amount of fluoroquinolones in the concentration range from 3.2×10^{-8} to 2×10^{-5}mol L^{-1}, with R^2 = 0.9995 and the limit of detection 2.4 × 10-8 mol L^{-1}.

The proposed voltammetry sensor was employed to the quantification of NF, OF, LF and GF, in pharmaceutical formulations and spiked human urine samples. The recovery from pharmaceuticals samples of NF, OF, GF, and LF was found as 98.55 ± 0.64, 98.52 ± 0.058, 98.55 ± 0.057, and 97.9 ± 0.052, respectively. The average recoveries of NF, OF, GF, and LF from the urine samples were found from 97.00% to 101.2%.

6.2.3. Hydroquinone (HQ)

For the Aβ-CD modified PNAANI, GCE was developed [102], and, to improve conductivity, MWNTs were applicable. Based on the analytical performance towards the HQ of the β-CD/PAA/MWNTs film, it was shown to be better than the another studied modifications of electrodes, owing to the synergistic influence of MWNTs and conducting PNAANI polymer and the accumulation effect of β-CD. The anodic currents increased with a linear concentration range from 1×10^{-6} to 5×10^{-3}mol$L^{-1}$of HQ, and the LOD was 8×10^{-7}molL^{-1}.This voltametric sensor exhibited excellent stability, reproducibility, and recovery for the determination of HQ.

6.2.4. Ascorbic Acid (AA)

Based on molecular recognition, the new ITO (indium tin oxide) modified electrode for ascorbic acid determination was prepared [103]. To this order, the ITO plate was coated with a monolayer of ferrocene residues (Fc-ITO), then through the supramolecular assembly of β-CD, was capped with Au nanoparticles(NRs) (βCD-nanoAu), and the functionalised electrode (β-CD-nanoAu/Fc-ITO) was achieved. The immobilisation of βCD-nanoAu on the Fc-ITO was evidenced by the AFM method and CV. Furthermore, the immobilisation of Au NRson on the electrode's sur-

face, improved electron transfer and consequently the amplification of the current.

The electro-catalytic activity toward ascorbic acid (AA) was evaluated by its electro-oxidation The linear dependence between the anodic peak and the concentration of AA exists in the range of 5.3×10^{-5} to 3.0×10^{-3}mol L^{-1},with a limit of detection (S/N=3) 4.1×10^{-6}mol L^{-1},with R^2= 0.9993. The selectivity towards dopamine that can be oxidised at the potential close of that to ascorbic acid was acquired. The two peaks 0.572V and 0.934 V are separated, obviously, in 0.1 M $LiClO_4$ at scan rate: 0.1 V s^{-1}.

6.2.5. Anagrelide (ANG)

Two voltametric methods of CV and DPV using β-CD modified CPE (CDMCPE) were developed [104]. The voltamograms for 3.0×10^{-9}mol L^{-1}ANG in a BR buffer solution of pH 3.0 at (CDMCPE), with times of accumulation of 150s and a potential of accumulation of -0.4 V, was registered. This sensor shows a linear response in the range 1.8×10^{-9} to 1.6×10^{-6}mol L^{-1}. The limit of detection (LOD) and limit of quantisation (LOQ) were found to be 2.2×10^{-8} to 0.733×10^{-7}mol L^{-1} with R^2= 0.9916. The offered sensor has been employed for the determination of ANG in spiked commercial available drugs (with recovery 97%-99%), human serum sample (with recovery 9%5-97%) and urine samples (with recovery 97%-99%).

6.2.6. Donepezil

A previous procedure of voltametric determination of donepezil has been investigated using ß-CD modified CPE electrode (CDMCPE) [105]. The effect of the accumulation potential that it covered was in the range of -0.1 to -0.8 V for 3.0×10^{-9}mol L^{-1} of in a BR buffer solution of pH=3.0) and an accumulation period of 150s was studied. The elaborated peak current was established at a maximum potential of -0.4 V. Moreover, the different practical parameters, those that directly influence the electrochemical response, such as pulse amplitude, stirring rate, scan rate, and rest period, are optimised using CV and DPV. The calibration curve equation was obtained Y(μA) = 0.2980 X + 0.02909 in the linear range of 3.2×10^{-9} to 4.2×10^{-8}mol $L^{-1}$of donepezil. The limit of detection (LOD) and limit of quantification (LOQ) were established to be 1.2×10^{-9} and 0.40×10^{-8}mol L^{-1}. Donepezil was determined in the other spiked samples of pharmaceutical, urine and serum samples, with the mean recovery of 98.49%, 98.82%, 98.85% respectively, and RSD 0.5-1.49.

6.2.7. Ascorbic Acid, Dopamine, Nitrite (AA, DA, NO2-)

A new sensor was developed to simultaneous determine DA, AA and NO_2^- based on (GS) and (MWCNTs) dissolved in the mixed solution of CD and cyclodextrin pre-polymer (pre-CDP) [106]. The MWCNTs effectively improved the electrochemical signal of the modified electrode, inhibited the assembling of individual GS and increased the employing of GS based composites. The inclusion reaction ability of CD and π-π stacking interaction between GS-MWCNTs surface and detected molecules were examined as to the reason of the efficiently simultaneous detection of AA, DA and NO_2^-. Under optimal conditions, the compounds can be analysed in the ranges of 5μM-0.48mM, 0.15-21.65μM and 5μM-6.75mM, respectively.

The electrode was utilised for simultaneously determination of AA, DA NO_2^- in human urine samples with recoveries between 95%-106% without any pretreatment steps except of dilution with PBS buffer of pH=6.0.

6.2.8. Glimepiride (GM)

Carbon paste (CP) and glassy carbon (GCE) electrodes have been investigated for glimepiride determination, and the host-guest complex of β-CD with glimepiride PBS buffer of pH=7.0 has been proved [107].The stability constant of complex was determined by spectrophotometry and DPV methods.

6.2.9. Oxacillin

A molecularly imprinted electrochemical sensor, based on a tin oxide electrode decorated with imprinted sol-gel film and β-CD incorporated multiwalled carbon nanotubes, cobalt nanoparticles-chitosan was developed for the sensitive and convenient establishment of oxacillin [108]. The covering of the electrode surface with the modifier (CoNPS-CTS/β-CD-MWNTs) was to improve the adsorption capacity of oxacillin, and the electrochemical signal thus increased the sensitivity. Results in the peak current of the electrode exhibited the possibility of oxacillin determination in the linear range of 2.0×10^{-7} to 1.0×10^{-4}mol L^{-1}, with the low limit of detection of 6.9×10^{-9}mol L^{-1}. To study the selectivity of the MIP film, some species co-existing with oxacillin in human blood were chosen.

The electrode was applied to the analysis of oxacillin in human blood serum samples of healthy people (with an oxacillin concentration of 4.7-6.1 mmol L^{-1}) and diabetic people (12.6 mmol L^{-1}). The yields of ox-

acillin were established by standard addition of pure oxacillin to the solutions containing the serum samples and are close to the values 95.9%-100.7% and RSD were in the range 1.2-3.1.

6.2.10. Tryptophan (Trp)

The GCE electrode for Trp was modified with β-CD functionalised Fe_3O_4 magnetic nanoparticles (β-CD-MNPs) [109]. The methods such as thermo-gravimetric analysis (TGA), FTIR and TEM were used to study the modification of the electrode surface. The electrochemical properties of Trp at the modified β-CD-MNPs electrode were proved by (CV) and electrochemical impedance spectroscopy (EIS), which shows that β-CD-MNPs successfully improved the electron diffusion between the surface of the electrode and the sample of the solution. As a result, using the nanoparticles coated with CD, the electrode offered interesting analytical performances as a large linear range from 8.0 × $10^{-7}$to 3.0 × 10^{-4}mol L^{-1} with a detection limit of 5.0×10^{-7}mol L^{-1} (S/N = 3) was observed. The relative standard deviation (RSD) of eight successive scans was 4.2% for 1.0×10^{-4}mol L^{-1}tryptophan. The procedure of determination of tryptophan was elaborated in pharmaceuticals containing an amino acid injection with pH=7.0 in PBS buffer. The obtained result of the determination by the presented sensor was very similar (1.45±0.04 g L^{-1} (n = 3), with the declared, certified value (1.40 g L^{-1}).

6.2.11. Ascorbic Acid and Uric Acid

A GC bare electrode modified by a β-CD entrapped in PETI film was prepared [110]. The surface was modified using the SWV. The modification of the sensor was proved to separate the voltametric peaks of uric acid and ascorbic acid, both of which were present in the same solution. The current peak of AA at UA = constant, increased linearly with R^2 = 0.996. The current peak of UA is increased in the concentration range (R^2 = 0.992) at AA = constant. The results obtained from FTIR measurements proved the formation of host-guest complexes.

The proposed sensors were favourably applied for the quantity of AA in commercial pharmaceutical preparations with a limit of detection of 0.22 μM.

6.2.12. Nifedipine (NIF)

Employing β-CD and CNTs as modifiers in a carbon paste electrode, a new sensor has been obtained for the electrochemical determination of NIF, employing adsorptive differential pulse stripping voltammetry (DPAdSV) [111]. The various methods, CV, EIS and DPASV, were employed to the electrochemical behaviour of the drug and SEM was utilised for the characterisation of the surface electrode. The calibration plot for β-CD-CNT-PE is acquired to be linear over the range 4.77×10^{-8}-2.00×10^{-5}mol L^{-1} with a linear regression equation as Ip(μA) = 3.931 C (μM) + 0.139, correlation coefficient 0.9980 (n = 5), and a LOD of 1.48×10^{-8}mol L^{-1}(RSD. = 0.36%).

The analytical application consisted in determining the concentration of nifedipine in pharmaceutical samples, urine and blood serum. The recovery of pharmaceutical formulations (5mg, 20 mg) is observed to be in the range of 99.09%-99.95%. An estimation of NIF in biological fluids from healthy volunteers was performed and found to give a percentage recovery in the range of 99.23%-98.99%.

6.2.13. Folic Acid (FA) and Uric Acid (UA)

Simultaneous determination of FA and UA in the presence of AA was acquired by using a modified GCE sensor based on poly(3-, 4-ethylenedioxy- thiophene) (PEDOT) and β-cyclodextrin functionalised SWCN [112]. The electrode was fabricated for the following steps: 1) preparation of GCE electrode, 2) β-CD-SWCNT suspension tipping onto the surface, 3) PEDOT deposition using chronoamperometry, 4) washing with double-distilled de-ionised water. The electrode provided the electrocatalytic oxidation current for the FA, UA, and AA mixture. The possibility of catalytic layer modifier could be attributed to the synergistic reaction of β-CD-SWCNT and PEDOT. The concentration ranges of 1-1000 μM with a detection limit (S/N = 3) of 0.8 μM for FA were achieved. For UA, the relatively lower range of 0.1-500 μM and a limit of detection 0.07 μM were obtained. The sensor was applicable for the determination of FA and a given recovery of 99.5%-108%, RSD 1.27%-3.01 % and 99%-108.5 %, RSD 1.52%-3.89% respectively.

6.2.14. Lisinopril

The new GC electrode, modified with β-CD graphene oxide-SO_3H, was investigated [113]. CV, DPV and chronocoulometry were utilised to examine the electrochemical properties of lisinopril at the electrode's surface. The CV results show that the β-CD/GO-SO_3H/GCE electrode can remarkably increase electroactivity toward the reaction of oxidation of lisinopril in a PBS solution of pH=6.0. A particular role of electrochemical oxidation is attributed to the cyclodextrin. The value of oxidation peak current of

lisinopril was 23 μA. A linear concentration range for lisinopril is close to the range of 0.21-190.4 μM. The linear equation was Ip(A) = 0.0093C (μM) +0.3852 (R2 = 0.9927). The limit of detection was estimated to be 0.11μlM (S/N = 3). The electrode exhibits good repeatability (the sensor can be stored in the atmosphere for about 1 month, with RSD of repeated peak currents of 4.7% and stability onto the DPVs measurements. The method was successfully used to assay the drug in human serum with yields to be in the range of 97.1%.-105.0%.

6.2.15. Singular

A novel selective, simple and reliable adsorptive and affinity linear sweep stripping voltametric method was developed for the assay of Singular [114]. The GCE electrode was obtained as in the previously described papers. An i*n situ* mercury film electrode was made up by the pippeting of the phosphate buffer into the cell, followed by the simultaneous depositing of Singular and mercury (II) onto GCE. Singular become soluble in aqueous solution by inclusive interaction with HPβCD. A method of cyclic voltammetry was used to study the kind of redox process that it would produce. The results showed that this sensor offered interesting analytical performances as it had a linear concentration range between 1.0 (0.61 fg/L) - 80.0 nM (3.04 ng/L), with a standard deviation of SD = 0.0031. Reproducibility controlled seven measurements per day for three consecutive days of 0.01 μM singular, under optimal conditions; the SD of 0.073 was obtained.

6.2.16. Nikardipina

The electrochemical oxidation of nikardipina was studied on a GCE, β-CD incorporated MWCNT modified electrode end, and the determination of the drug has been additionally revised by the host-quest complex formation with β-CD [115]. The effect of the pH solution (0.04 M NaOH), preconcentration potential (-0.9V), time (1 min) and scan rate (20 mV/s.) were researched on the peak current for nikardipina. The surface morphology of MWCNTs-β-CD film was described by using the EIS method. The linear range of calibration curve closed in the range 1.0×10^{-7} to 2.0×10^{-5}mol L^{-1}. The limit of detection was obtained as 1×10^{-8}mol L^{-1}. The effect of the drug assay proved that this sensor has excellent sensitivity (the curve of calibration as $\Delta Ip(nA) = 34.84 + 117.6c_{nicardipine}(\mu M)$, and selectivity shows good accuracy and precision.

The percentage yields from blood serum samples acquired from 97.6% to 110%.

6.2.17. Amantadine (AMD)

The next papers [116] are associated with the investigation of the CP modified electrode with β-cyclodextrin (β-CD/CPE) for voltametric determination of the antiviral drug amantadine. Fc was used as an electrochemical probe, which interacts with-β-CD, making a host-quest complex at the electrode surface. Then, electrochemically inactive AMD can replace ferrocene in the cyclodextrin cavity; a decrease of current resulted. The range of linearity of the calibration curve reaches from 0.1 to 1.0 mM of amantadine and a detection limit of 0.08 mM was achieved. The repeatability and reproducibility of the method was investigated with RSD 0.25%-0.35% and ±2.8% respectively.

The modified sensor was successfully applied in the determination of AMD in pharmaceuticals in tablet form with an established recovery of 96% ± 1 %.

6.2.18. Acyclovir

A sensor based on polymerisation of β-cyclodextrin modified PGE electrode was elaborated [117]. The successful modification of the electrode surface layer was demonstrated by Scanning Electron Microscope images. The anodic current proportionally depends on the concentration of AC in two linear concentration ranges of 5×10^{-8} to 6×10^{-7}mol L^{-1} and 1×10^{-6} to 9×10^{-6}mol L^{-1} with the limit of detection 7.59×10^{-9}mol $L^{-1}$of ACV. The modified electrode was used to the quantitative assay of AC in pharmaceutical products and human urine.

The SWV method has been favourably applied to pharmacokinetic researches of ACV in healthy people after oral application of a single amount of Zovirax suspension (400mg/5 mL).

6.2.19. Paracetamol

The electrochemical properties of paracetamol were investigated on modified β-CD/RGO electrodes because of the high supramolecular recognition and enrichment ability of β-CD and the excellent electronic properties of RGO sheets. [118]. The modification of the electrode was utilised with FTIR, UV-VIS spectroscopy, Raman spectroscopy, TEM and SEM methods. Amperometric determination led to a concentration linear range close to 0.01 to 0.8 mM with a limit of detection 2.3 μM. The sensor was proved to have a satisfactory anti-interference property and acceptable reproducibility.

6.2.20. Isoquercitrin and Baicalin

In this research [119], a facile method was successfully applied to obtain DM-β-CD (2-, 6-dimethyl-β-

cyclodextrin) functionalised graphene hybrid nanosheets DM-β-CD. This new nanocomposite embedded on GCE allowed it to receive electrodes to detect two flavonoid drugs (isoquercitrin and baicalin). The linear ranges of isoquercitrin and baicalin were 10nM-3.0 μM and0.04μM-3.0 μM, with the detection limits of 4nM and 10nM, respectively. The sensors show favourable characteristic of simple construction, cheapness, high sensitivity, good reproducibility and stability.

The electrodes were utilised for the assay of flavonoids in real human serum samples, with a recovery of 96.9%-105% and 97.2%-103.3% of isoquercitrin and baicalin respectively.

7. REVIEW ON BIOSENSORS IN BIOMEDICAL ANALYSIS

Voltametric and amperometric biosensors have relatively better properties over other existing measurement methods, because they can offer simple, non-complicated and low-cost on-field quantity detection.

The most intensely investigated biosensors are enzyme electrodes because they have greater sensitivity and selectivity, and respond quickly to the typical, specific molecules of a substrate. Moreover, the performance of an enzyme sensor depends on the specified method of enzyme immobilisation when constructing a biosensor. Different enzyme immobilisation approaches have been utilised, including covalent binding, adsorption and the cross linking of an appropriate enzyme and entrapment in gels or polymer layers. Some of these methods are critical in various enzyme biosensors. In the result of physical adsorption on GC or CP electrodes, the sensors have low reproducibility. More recently, sensitive biosensors with supramolecular architecture were constructed. The host molecules, especially the cyclodextrins, are three dimensional matrices and can be effectively retained organic molecules in their action and immobilisation processes. Furthermore, the chemical modification of enzymes with CDs yields biocatalysts with noticeable stability. Supramolecular immobilisation occurs on metal surface electrodes *via* host-quest associations of chemically modified enzymes.

The examples of immobilisation process of cyclodextrins based biomolecules are presented in Figs. (**7** and **8**).

Besides primarily glucose, xanthine, DNA and other compounds were detected by the means of electrochemical biosensors. Several examples are demonstrated in Table **2**.

Furthermore, there are a lot different papers and reviews concerning these supramolecular procedures. Immobilising proteins (cytochrome) on metal surface coated with self assembled monolayers of β-cycyclodextrins are presented in paper [152], immobilisation enzymes *via* host-quest interactions in thin film polymers for H_2O_2 biosensor [153], xanthine biosensor [154], The very interesting issues on cyclodextrins in enzyme technology or using neoglycoenzymes in the chemical and clinical analysis are presented in reviews [155, 156] respectively.

CONCLUSION

In the area of biomedical and pharmaceutical analysis, various types of electrochemical sensors especially based on carbon materials (CNT-s, MWCNTs, GCE and GS), modified with cyclodextrins, still belong to the most popular sensors. Cyclodextrins and their derivatives, due their properties are, increasingly, being used for the preparation of the voltametric and potentiometric modified electrodes.

Generally, compared with other electrochemical (bio) sensors, potentiometric devices modified with cyclodextrins, carbon nanomaterials or cyclodextrins-nano-composites achieved a much better sensitivity than the other non-modified electrodes. This may be attributed to host-quest interaction and encapsulation of drug molecules into the lipophilic cavity of cyclodextrins. The modified electrodes show a ten-fold lower LOD, shorter response time, and a sometimes lower operational lifetime, because of a lesser degree of leaching components into a soaking solution. In the case of the (voltametric amperometry) sensors, the effect of modification with cyclodextrins improves the kinetics of the electrode process and enhances the accumulation of the analyte at the surface. In results, it contributes to the increase of the sensitivity of the electrode. The modified electrodes have high selectivity, good stability and good reproducibility.

As regards difficulties, preparation of nanocomposites with cyclodextrins or preparations of the entire electrode seem time-consuming at times. Even so, the electrochemical measurements exhibit low cost, high sensitivity, sufficient selectivity, wide versatility (in materials) with a high functionality of application in real and model samples. These sensors are a good alternative to the other expensive methods *e.g.* chromatography, spectral methods and others.

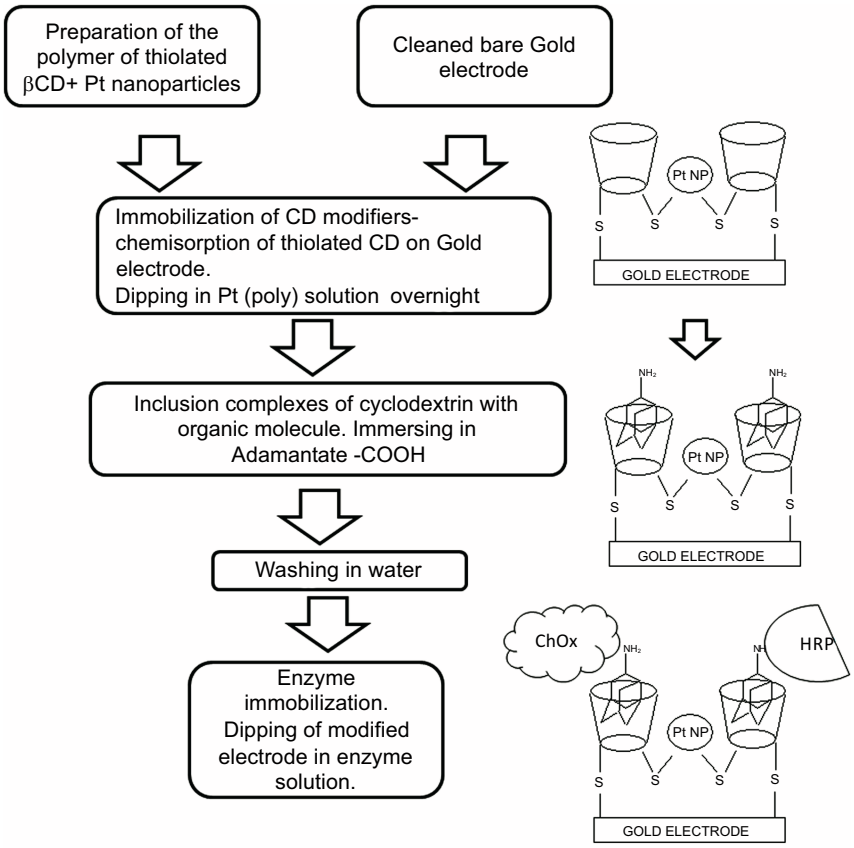

Fig. (7). Preparation of a biosensor surface with supramolecular architecture Au/PtpolyCD/ADA/Enzyme.

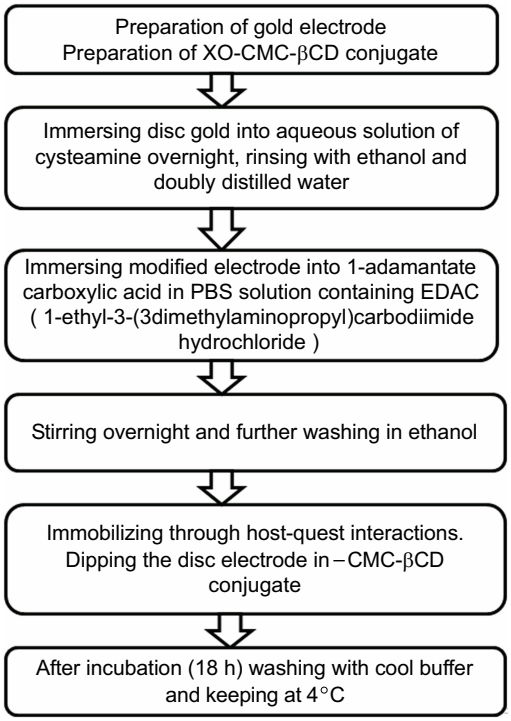

Fig. (8). Scheme for the preparation of an Au -ADA electrode immobilised with supramolecular mediated of CMC-CD-XO (carboxymethyl cellulose-cyclodextrin-xanthine oxidase).

The general trends involving the design and the development of new electrochemical sensors are as follows:

- The discovery of new pharmaceuticals and biological molecules which is one of the most dynamic areas of research in medical and pharmaceutical area.
- In potentiometry development of new possibilities for construction of solid contact electrodes, the use of new nanomaterials in membranes, composites with cyclodextrins as ion-sensitive substances.
- Striving for improvement of parameters of the function of voltametric electrodes through the use of nanomaterials, (nanomolecules, carbon nanotubes, graphene) improving the electrochemical signal.
- In the case of the development of biosensors of the biomimetic receptor system cyclodextrin, crown ethers, calixarene, molecularly imprinted polymers capable of binding target molecules with affinities specified as a natural receptor.

Table 2. Electrochemical biosensors for biomolecules assay.

Analyte	Electrochemical Detection, and Type of Biosensor	Construction of the Biosensor	LRD (LOD)	Remarks	Ref(s).
AFP (clone Nos. A14C11 and A46C9)	DPV immunosensor (sandwich type)	SH-β-CD/ AuNRs/Ab/chitosan/PDDA/ CNT/GCE	0.5 pg /mL 0.5 ng/mL (0.032 pg/ mL)	Serum tumour marker, 0.02M PBS buffer, pH=7.4	[120]
Immunoglobulin G (HIgG)	SV, immunosensor	β-CD functionalised gold nanoparticles (AgNPs) immobilization with Ag@BSAbionanoprobes	1 fg/ mL-10 pg/ mL (0.5 fg/mL)	Real serum samples	[121]
Xanthine	Amperometry, enzyme sensor	Xanthine oxidase modified with β-cyclodextrin-branched CMC immobilised on Au/1-adamantanyl XO/ CMC - β-CD/ADA/Au	300 μM -10.4 mM (200 μM)	Model samples, 0.1M PBS buffer, pH=7.0	[122]
Glucose	Amperometry, enzyme sensor	GNPs/MT-β-CD-Fc/GOD	0.08-11.5 mM (15 μM, S/N = 3)	Human plasma, PBS buffer pH=7.0	[123]
Glucose	Amperometry, enzyme sensor	GOD/CNT-CDP/GCE-	0.004-3.23mM (3.5μM)	Model samples pH= 5.6-7.8	[124]
Cholesterol	CV, amperometry, enzyme sensor	1) MB/β-SH-CD/AuNPs/Au, 2)ChOx/MB/β-CD/AuNPs/Au MB-methylene blue	2.0×10^{-8}- 5.0×10^{-5}M (7×10^{-9}M)	Model samples, 20 mM PBS buffer pH=7.0	[125]
Glucose	CV, amperometry, enzyme sensor	GOD-ADA/β-CD-PAMAM/PtNP/Au PAMAM cystamine core G-4 dendrimer.	5 -705 μM (2.0 μM)	pH=6.0-7.0	[126]
l-phenylalanine	CV, amperometry, enzyme sensor	β-CD Au coated electrode immobilised with PheDH-ADA (adamantate modified phenylalanine dehydrogenates)	20μM -3mM (15 μM)	Glycine/KCl/ KOH buffer pH=10.4	[127]
H_2O_2, Glucose	CV, amperometry, enzyme sensor	GOD/PTy/SBCD/PtNP-modified BDD electrode	up to 10 mM (10 μM)	PBS buffer, pH=7.0	[128]
H_2O_2	CV, amperometry, enzyme sensor	Peroxidazemodified with ADA or 1-mono-6-butylenediamino-6-deoxy-β-cyclodextrin-branched CMC residues	125 - 600 μM (2 μM)	PBS buffer, pH=7.0	[129]
Dopamine	CV, amperometry, enzyme sensor	SPE/MWCNT/β-CD/GOD	10-50μM (0.48±0.02μM)	PBS AT pH=7.44	[130]
Choline	SWV, enzyme sensor	Au/PtpolySH-β-CD/ADA/E (bienzyme ChOx and HRP	10^{-9}-10^{-2} M down to 0.1 nM	0.1 M PBS pH=7.0	[131]
Quercetin	SWV, enzyme sensor	CP/ BLacImm/AgNP-BMI.$Tf_2N$with Lac immobilised on β-cyclodextrin modified with epichlorohydrin (β-CDEpi)	0.499-7.407 mM (0.037±0.004 mM)	Real samples-pharmaceutical, acetate buffer (0.1M pH=4.0)	[132]
DNA	DPV	α-CD/MWCNT/GCE with PbS nanoparticles and dabcyl-labelled hairpin probe DNA	8.3×10^{-7} - 8.3×10^{-1}M (7.1×10^{-10} M)	Model samples, pH=7.0M	[133]

(Table 2) contd…

Analyte	Electrochemical Detection, and Type of Biosensor	Construction of the Biosensor	LRD (LOD)	Remarks	Ref(s).
DNA	Amperometry, enzyme electrode	The self-assembled gold electrode modified SH-βCD/Fc-CMC-DNA, peroxidaze	0.26.5mgL^{-1} (0.02mg/L) 10 pM	1mM H_2O_2in 0.1 M PBS + 0.15 M KCl (pH=6)	[134]
Glucose	CV, amperometry, enzyme electrode	The self-assembled Pt electrode modified MWCNT/1/βCD-tagged GOD 1-tris[4-, 4-bis(4-pyren-1-ylbutyloxy)bipyridinyl)] iron(II) complex	1.5 μM	Model samples 0.1 M PBS buffer pH=7.0	[135]
Xanthine	CV, amperometry, enzyme electrode	XO-adamantate/SWNT/Pyr-βCD/GCEPyr-βCD	5.0-600mM (2 μM)	0.1 M PBS buffer pH=7.0	[136]
Dopamine, ascorbic acid nitrite	CV, enzyme electrode	GS/pre-CD polymer (CDP) /MWCNT modified GCE electrode	0.15-21.65 μM 5 μM-0.48 mM 5 μM-6.75 mM (0.05 μM) (1.65 μM) (1.65 μM)	Human urine samples, 0.1 M PBS buffer pH=6.0	[106]
Antigliadinantibodies	CV, amperometry, immunosensor	CDPSH/ADA-CMC-GLI modified gold electrode with mouse anti-IgG-HRP carboxymethylcellulose (CMC)	0 to 0.75μ g/mL (20 ng/mL)	Human serum samples PBS buffer pH=7.0	[137]
DNA	CV, DPV, enzyme electrode	CdS nanoparticle-dsDNA /β-CD/ACNTs modified GCE electrode	1.0×10^{-7}- 1.0×10^{-12} M (5.0×10^{-13} M)	Model samples, phosphate-buffered saline PBS buffer 0.1 M pH=7.0). Acetate buffer 0.1 M pH=5.2	[138]
Cathecol. Xanthine	CV enzyme electrode	CPE modified with Fe_3O_4@APTES-CD:TYR(tyrosinase) Fe_3O_4@APTES-CD:XO	100 nM-12 μM (22nM) 5.0-120 μM (2μM)	Model samples PBS buffer, pH=7.0 (XO), pH=7.5 (TYR)	[139]
Xanthine	Amperometry enzyme electrode	XO-CD/ pAuNP/SWNT/GCE	50 nM - 9.5μM (40nM)	Model samples, PBS buffer pH=7.0	[140]
Thrombin	DPV aptasensor	CdS@-CDs/DB modified Au electrode	7.3×10^{-12}- 7.3×10^{-9}M (4.6×10^{-12} M)	Samples of Thrombin aptamer, PBS buffer 0.1 M, pH=7.0), sodium acetate buffer 0.1 M pH=5.3	[141]
DNA guanine (G) and adenine (A)	SV, enzyme electrode	(CD/PNAANI/CNTs/ SPE)	0.01 - 1.02 mM (5.0 μM)	Calf thymus double stranded DNA (dsDNA) samples, PBS buffer, pH=7.5; 7.4	[142]
Glucose	CV, enzyme electrode	GOD/CD/PAT-Au@ modified CCE electrode	0.25 mM- 16.0 mM (0.09 mM (S/N = 3)	Model samples, PBS buffer pH=7.17	[143]

(Table 2) contd…

Analyte	Electrochemical Detection, and Type of Biosensor	Construction of the Biosensor	LRD (LOD)	Remarks	Ref(s).
Anti-gliadin anti-body	Amperometry, immunosensor bienzymaticam-perometric immunosensor	Au/1β/3 3-GLI/LOX GLI/ChOX GLI/GOX Fc/CMC carrier bearing a capture protein to the βCD modi-fied surface of Au	0-4 μg/mL (70 ng /mL)	0.1 M PBS + 0.15 M KCl pH=6.0	[19]
Glucose	Enzyme electrode	GOD/β-CD-SWCNTs/ CTAB/GCE	1.87 mM- 12.87 mM (0.484 mM/)	PBS buffer pH=7.0	[144]
Phenolic com-pounds (rutine, caffeic acid, cate-chin, fisetin, quer-cetin)	CWV, enzyme electrode	CPE/PPO/β-CDEP/Ir-BMI·PF6. (Ir-BMI·PF6)1-butyl-3-methylimidazoliumhexafluoro-phosphate; (β-CDEP) cyclodextrin modified with epichlorohydrin (EP)	1.3×10^{-7}- 2.0×10^{-6}M (7.9×10^{-8} M)	Model samples of rutine, PBS buffer 0.1M pH=7.0	[145]
Acetylcholine	Enzyme electrode	Acetylcholinesterase(β-CDEP /nano-PPCPE	5×10^{-6} M - 2×10^{-4} M (1.5×10^{-7})	-	[146]
Cholesterol	CV, enzyme elec-trode	PSBTz film with β-CD/ ChOx deposit on graphite electrode ChOx	0.15−22.5 μM (0.005 μM)	Serum samples, PBS buffer pH=7.0	[147]
Dopamine	CV, DPV, enzyme electrode	SPE/rGO-CDBA-Lac	0.1-70 μM (of 0.03 μM)	Human urine sam-ples, pH=7.0	[148]
Glucose	CV, AM enzyme electrode	RGO/β-CD /GOx/GCE	0.05 - 3.0mM (12μM)- CV 0.01 - 15.55mM (1.2μM) -AM	Blood serum sam-ples, PBS buffer pH=7.0	[149]
Biomarker CD40 ligand (sCD40L)	CV, DPV immunosensor	β-CD-rGO-TEPA-PDITC TEPA tetraethylenepentamine PDITC - 1.4-phenylene diisothio-cyanate (PDITC $C_6H_4(NCS)_2$)	0.25 to 50 pg /mL (83.3 fg mL)	Human serum samples, PBS buffer (pH =7.4)	[150]
Glucose	Enzyme electrode	GOD/CM-β-CDFcCA /RGO-Ag@ modified electrode	0.105 - 11.805 mM (0.035mM)	-	[151]

As a conclusion, the presented electrochemical sensors provide an interdisciplinary approach between analytical and medicinal chemistry. For the sake of many pharmaceutical, biomedical applications and the advantages of these sensors, further development of these device systems in the coming years is expected.

LIST OF ABBREVIATIONS

(TCT) = 2-, 4-, 6-trichloro-1- , 3-, 5-triazine

@ (NRs) = Nanoparticle

2-H3-TMAPβCD = 2- hydroxyl-3-trimethylammoniopropyl -β-cyclodextrin

6-TsO-β-CD) = 6-O-toluenesulfonyl-β-cyclodextrin

AA = Ascorbic acid

Ab = Antibody

ACNTs = Aligned carbon nanotubes

ACV = Acyclovir

ADA = Adamantane

Ag@BSA = Nanosilver-doped bovine serum albumin

AM = Amperometric method

AMD = Amantadine

APTE = 3-aminopropyl) triethoxysilane

APTMS = 3-amino-propyltrimethoxysilane

BDD = Boron-doped diamond

BMI.Tf_2N = Bis(trifluoromethylsulfonyl) imide

BR = Britton-Robbinson buffer

Bu4NPF6 = Tetrabutylammoniumhexafluoro-phosphate

CCE = Carbon ceramic electrode

CDAuNP = Cyclodextrin-functionalised gold nanoparticles

CD = Cyclodextrin

CDMCPE = Cyclodextrin modified carbon paste electrode

CDPSH = Thiolated- β-cyclodextrin polymer

CGE = Coated graphite electrode

ChOx = Cholinesterase

CMC = Carboxymethylcellulose

CMCD = Carboxymethyl-β-cyclodextrins

CNTs = Carbon nanotubes

CTAB = Cetyltrimethyl ammonium bromide

CV = Cyclic voltammetry

CWE = Coated wire electrode

DB = Dabacyl4-((4-(dimethylamino) phenyl) azo) benzoic acid

DM-β-CD = 2-, 6-dimethyl-β-cyclodextrin

DPAdSV = Adsorptive stripping differential pulse voltammetry

DPCV = Differential pulse cathodic voltammetry

DPV = Differential pulse voltammetry

EIS = Electrochemical impedance spectroscopy

EM = Electron microscopy

FA = Folic acid

Fc = Ferrocene

FcCA = Ferrocenecarboxylic acid

GCE = Glassy carbon electrode

GF = Gatifloxacin

GNPs = Gold nanoparticles

GOD = Glucose oxidase

GO = Graphene oxide

GS = Graphene sheets

HBβCD = Heptakis(2-, 3-, 6-tri-O-benzoyl)-β-cyclodextrin

HGO = Holey graphene oxide

HMβCD = Heptakis(2-, 3-, 6-tri-*o*-methyl)-*β*-cyclodextrin

HPβCD = Hydroxypropyl-β-cyclodextrin

HRP = Horseradish peroxidase

HAS = Human serum albumin

ITO = Indium tin oxide

K_{10} Mt = K_{10} Montmorillonite

Lac = Laccase

LDR = Linear detection range

LF = Lomefloxacin

LOD = Limit of detection

MB = Methylene blue

MNPs Magnetic nanoparticles

MT-β-CD = Mono-6-thio-β-cyclodextrin

MWNTs = Multi wallet carbon nanotubes

nano-PPCPE = Nano-porous pseudo carbon paste electrode

NaTFPB = Sodium tetrakis(4-fluorophenyl)borate

NF = Norfloxacin

OF = Ofloxacin

OSWAV = Osteryoung square-wave anodic voltammetry

PAMAM = Polyamidoamide

PANI = Polyaniline

PAT = Poly(4-aminothiophenol)

PBS = Phosphate buffer solution

PCMCD	=	Electro-polymerisation carboxymethyl-β-cyclodextrin
PEDOT	=	Poly-3, 4-ethylenedioxythiophene
PETIM	=	Polyethyleneimine
PGE	=	Pencil graphite electrode
PNAANI	=	Poly(N-acetylaniline)
PPO	=	Polyphenol oxidase
pre-CDP	-	Cyclodextrinprepolymer
PSBTz	=	Poly(2-(2-octyldodecyl)-4-, 7-di(selenoph-2-yl)-2H-benzo[d][1-, 2-, 3]triazole)
PtNP	=	Platinum nanoparticles PtpolyCD
Pty	=	poly(tyramine)
Pyr-βCD	=	Mono-6-ethylenediamino-(2-pyrene carboxamido)-6-deoxy-β-cyclodextrin
rGO	=	Reduced graphene oxide
S/N	=	Signal/noise
SBCD	=	Sulfobuthylether -β-cyclodextrin
SEM	=	Scanning electron microscopy
SH-βCD	=	thiolated-β-cyclodextrin
SPE	=	Screen printed carbon paste electrode
SWNT	=	Single-walled carbon nanotubes
SWV	=	Square wave voltammetry
Trp	=	Tryptophan
UA	=	Uric acid
XO	=	Xanthine oxidase
ZNRs	=	Zinc oxide nanorods

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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