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Adsorptive stripping voltammetry applied to drug analysis: a powerful tool*

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Abstract: A brief review of the principles and instrumentation of adsorptive stripping voltammetry is presented and the advantages of the method are described. As for many highly sensitive techniques applied to the analysis of complex media, severe interferences may occur. Different approaches can be used to circumvent these problems, exemplified by several applications in biological fluids. The application of modified electrodes to enhance selectivity is discussed.

Keywords: *Adsorptive stripping voltammetry; pharmaceutical compounds; trace analysis; complex media; modified electrodes.*

Introduction

Electroanalytical methods, in particular voltammetric techniques, are well established in pharmaceutical and biomedical analysis. However, the requirements of these techniques in clinical chemistry, toxicology and drug control laboratories increase as more potent compounds are developed which give lower therapeutic concentrations. Moreover, information concerning the absorption, distribution, biotransformation and elimination of pharmacologically active compounds is useful for detecting human diseases and for determining the bioavailability and the pharmacokinetic profile of a new drug or its metabolites. For this, highly selective and sensitive analytical methods are required. The introduction of potentiostatic devices and the application of new potential — time waveforms has resulted in voltammetric techniques that allow quantitative determinations at the 10^{-6} or 10^{-7} M level [1–5]. A further improvement of sensitivity has been obtained by applying an accumulation step which increases the amount of electroactive species at the electrode, allowing the technique to cover a 10^{-6}–10^{-10} M concentration range [6].

Principles

Among the techniques employing a preconcentration step, the first to be developed has been anodic stripping voltammetry (ASV), mainly applied to the trace analysis of

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heavy metal ions using a hanging mercury drop electrode (HMDE) or a mercury film electrode [7, 8]. Preconcentration is performed at a potential selected in the diffusion current region for a length of time depending on the solution concentration and under controlled stirring. After a rest period, the potential is scanned towards less negative values in order to release the amalgamated metal.

Cathodic stripping voltammetry (CSV) has been used to determine several organic compounds or anions such as halides, sulphide, selenide and some oxyanions that form insoluble salts with the electrode material, usually a mercury or a silver electrode [6]. The application of a relatively positive deposition potential results in the formation of an insoluble film on the electrode surface. The stripping step occurs during a negative potential scan, corresponding to the reduction of the cation at the electrode.

In addition to the above described techniques where the deposition step is performed through an electrolytic process, another method allowing preconcentration of organic compounds has been developed during the last 5 years. Numerous organic derivatives exhibit adsorption phenomena which are generally considered to have adverse effects on voltammetric measurements. In adsorptive stripping analysis (AdSV) however, this adsorption process is purposely used as a preconcentration step. As a result, a wide variety of substances possessing surface-active properties are easily measurable at the subnanomolar concentration level [6, 9–11].

The principle of the method can be compared to that of anodic or cathodic stripping, except that no charge is transferred during the preconcentration step (Fig. 1).

Accumulation of the compound at the electrode surface is performed at open circuit or by applying a suitable potential at which no electrochemical reaction occurs. After an equilibration time, the potential is scanned anodically or cathodically, depending on the redox properties of the compound and on whether it contains a reducible or oxidizable group. In some cases of electroinactive derivatives, a tensammetric peak can be recorded.

Instrumentation

The instrumentation is the same as for ASV or CSV and a commercially available

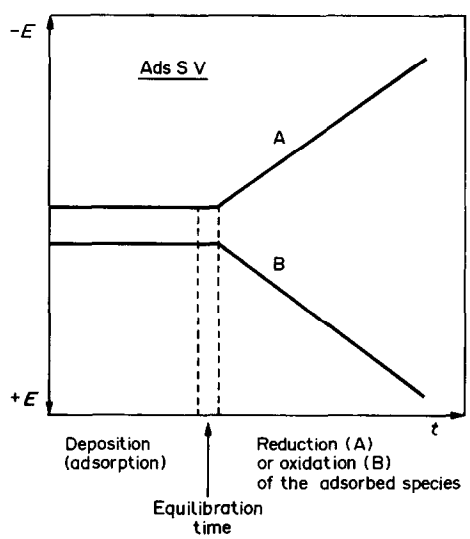

Figure 1
Potential–time sequence used in DC AdSV. A, reduction process; B, oxidation process.

polarograph can be used. However, a computerized instrument with automatic timing of the successive operations is useful for this purpose.

AdSV can be performed with any electrode used in direct voltammetry, provided that a reproducible and constant surface area can be ensured during a series of measurements. When the adsorbed layer is to be reduced, the HMDE remains the best choice since the drop is renewed after each scan with high reproducibility when an automatic stand is used. Oxidation processes require a metallic or carbon solid electrode. Platinum and glassy carbon electrodes have been proposed as well as carbon paste electrodes, the surface of the latter being more easily renewed by removing the surface layer of the paste. Reproducibility is however not as good as that of the HMDE which also gives lower detection limits.

It should be noted when using a carbon paste electrode that the compound can be accumulated not only as a result of adsorption but also by dissolution in the pasting liquid of the carbon paste. In some applications of the technique the proper choice of the pasting liquid may lead to higher selectivity.

Chemically modified electrodes have received great attention in electroanalysis [12, 13]. These modified surfaces have been widely used to provide enhanced selectivity and sensitivity and numerous applications have been described in various fields such as electrocatalysis, biosensors or potentiometric measurements, and also for selective preconcentration of different analytes [14]. However, the preparation of such electrodes by chemisorption or covalent bonding gives rise to low active site density, poor reproducibility and short life times. Moreover, the covalent bonding procedure is tedious and time consuming. For these reasons, a greater attention has been paid to polymer film electrodes which exhibit higher reproducibility, activity and stability, as well as to carbon paste electrodes which can be modified by incorporation of the modifying compound into the carbon paste matrix. Such a procedure allows the incorporation of various modifiers including organic and inorganic polymers, ion exchange resins or insoluble compounds.

During the stripping step, different waveforms can be applied in order to enhance the voltammetric response. Differential pulse [2, 3] and square-wave [4, 5] modes are often

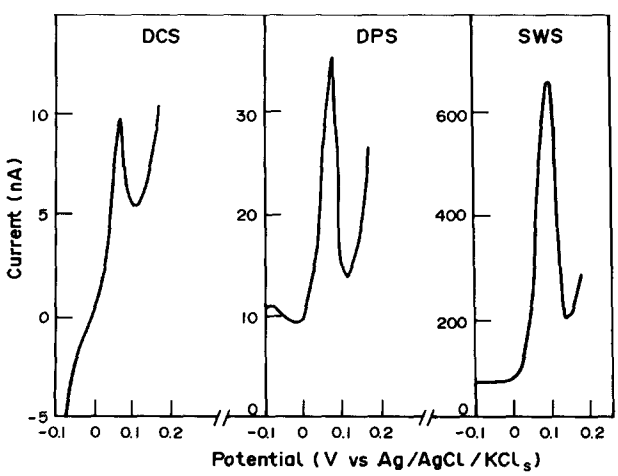

Figure 2
Comparison of the responses obtained using DC, DP and SW stripping voltammetry. Vitamin K_3, 5×10^{-8} M; $HClO_4$ 0.3 M; t_{acc} = 60 s; E_{acc} = −0.100 V; scan rate (mV s^{-1}); DCS, 20; DPS, 10; SWS, 200; DPS and SWS pulse amplitude, 20 mV; SWS frequency, 100 Hz (from ref. 16).

selected as they increase the signal-to-noise ratio (Fig. 2). Linear scan and alternating voltage [1] modes have also been proposed.

Advantages

With regard to direct voltammetry, adsorptive stripping techniques exhibit some additional advantages. Since a great number of organic compounds including pharmaceutical and biological substances exhibit surface-active properties, they can be determined at very low levels, generally ranging from 10^{-6} to 10^{-10} M. Moreover, several metal ions which can be reduced at mercury electrodes cannot be amalgamated or exhibit an irreversible metal–metal ion couple, extreme redox potentials or formation of intermetallic compounds. They can be analysed after their complexation by some surface-active organic ligand followed by their adsorptive collection at the electrode surface and the subsequent reduction of the adsorbed layer. As the analytical concentrations are very low, aqueous solutions may be used, increasing the adsorption capability of most organic compounds.

Interferences

Several interferences may occur, mainly when complex or biological samples are analysed. They result from the presence of other surface-active species in the sample solution.

Selectivity can be improved by a modification of the deposition potential or by changing a solution parameter e.g. pH, supporting electrolyte or solvent addition. The problem of high levels of less adsorbable electroactive components, sometimes resulting in overlapping peaks, can be solved by using a medium exchange procedure: the accumulation step is performed in the complex medium, then the electrode is transferred to a more appropriate supporting electrolyte for the stripping step. Such a procedure however is to be used only with solid electrodes or the MFE, since the HMDE is not mechanically stable enough. Another way to solve this problem, which occurs mainly when biological fluids are investigated, but again only when solid electrodes are used, is to cover the electrode surface with a porous membrane which acts as a barrier towards molecules of high molecular mass but allows the smaller molecules to reach the electrode surface. Such a method avoids inhibition of the electrode and increases selectivity.

More generally, surface-active species in the sample may significantly interfere in adsorptive stripping measurements. These species can affect the accumulation via a competitive coverage of the electrode surface, resulting in depletion of the stripping peak. These problems may be minimized by various approaches. Small reductions in the magnitude of the peak can be corrected by using the standard addition method, shorter accumulation times or by a proper choice of the accumulation potential. More severe peak depressions require a preliminary chromatographic separation of the interfering surfactants.

The elimination of surfactant interferences from natural water samples in which metal ions are to be measured can be performed by UV irradiation prior to adding the complexing agent; sample acidification is recommended to minimize losses by adsorption on the walls of the quartz tube. Alternatively, interferences from reducible metal ions can be eliminated by adding ethylene diamine tetra-acetic acid (EDTA).

Methodology

In order to decide if adsorptive stripping voltammetry should be used, a direct voltammogram of the compound should be recorded. This should be repeated after imposing the initial potential during a 60-s period under stirring conditions. A comparison of the curves will immediately show a substantial increase of the peak current if the compound has been accumulated at the electrode surface (Fig. 3).

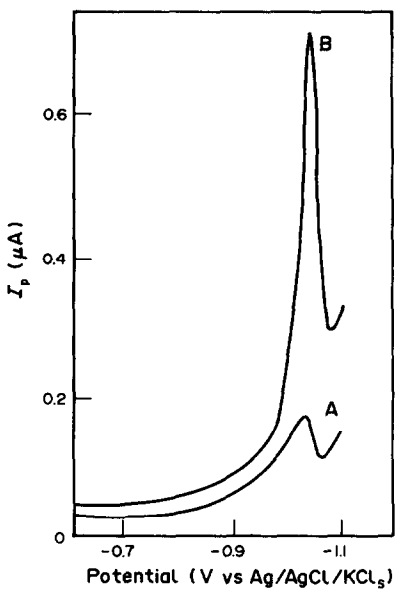

Figure 3
Peak enhancement resulting from the accumulation step. SWS voltammetry of piroxicam 1×10^{-7} M; H_2SO_4 0.05 M; A, $t_{acc} = 0$ s; B, $t_{acc} = 60$ s (from ref. 77).

To achieve maximum sensitivity, optimum conditions should be utilized. The adsorption process depends on many variables such as the solvent, the nature and the concentration of the supporting electrolyte, pH, mass transport and temperature and on the deposition potential. However, these parameters may also influence other properties of the voltammetric response such as reproducibility or peak shape and in most cases, a compromise should be made between sensitivity and reproducibility.

Adsorptive stripping procedures generally utilize aqueous solutions since most neutral organic analytes are adsorbed as a result of hydrophobic forces. With aqueous solutions, the analyte concentration remains sufficiently low to avoid solubility problems and the addition of organic solvents is to be considered only when interference problems occur.

The influence of pH should be investigated since adsorption processes strongly depend on this parameter. Significant enhancement of the peak can result from the selection of the optimal pH value as can be seen from Fig. 4.

The choice of the supporting electrolyte is also of great importance since it can affect the intensity and the shape of the peak, which is represented in Table 1 by the half-peak width, as well as its reproducibility [15] (Table 1). In some cases where a buffer is not required, it is more convenient to use a simpler supporting electrolyte known to be non-adsorbed, e.g. sodium perchlorate or dilute acids or bases. This generally enhances sensitivity.

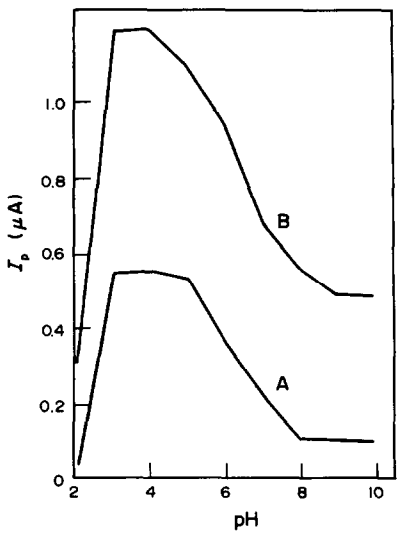

Figure 4
Influence of pH on the peak current of marcellomycine. A, 1×10^{-7} M; B, 2×10^{-7} M; SWS voltammetry; acetate–phosphate–Tris–HCl buffer 0.03 M; t_{acc} = 60 s (from ref. 15).

Table 1
Peak intensity (I) and half-peak width ($W_{½}$) of the SWS voltammetric response of a 2×10^{-7} M marcellomycin solution using different pH 7.0 buffers

Buffer	Acetate	Phosphate	Citrate	Tris–HCl	Borate
I (μA)	0.65	0.43	0.26	0.72	0.20
$W_{½}$ (mV)	95	85	80	100	75

Buffer concentration, 0.03 M; t_{acc} = 60 s (from ref. 15).

Table 2
Influence of the buffer concentration on the peak current and on the half-peak width of a 1×10^{-7} M marcellomycin solution

Buffer conc. (M)	1×10^{-3}	3×10^{-3}	1×10^{-2}	3×10^{-2}	1×10^{-1}	3×10^{-1}	1
I (μA)	0.05	0.24	0.65	0.50	0.09	0.01	0.005
$W_{½}$ (mV)	220	155	125	75	70	72	68

Acetate buffer pH 4.5; SWS; t_{acc} = 60 s (from ref. 15).

The ionic strength of the supporting electrolyte may play a significant rôle by its influence on the shape of the recorded peaks and on the amount of accumulated material [15] (Table 2). These solution parameters are characteristic of each analysed compound and must be determined in each case.

Several operating parameters are also to be investigated. The accumulation should proceed at the potential of maximum adsorption. For neutral molecules, a potential corresponding to the electrocapillary zero value is generally favourable and an open-circuit accumulation may be performed. However, when the charged or neutral character of the molecule is not known, it is often better to record several voltammograms after the accumulation has been performed at different potentials (Fig. 5).

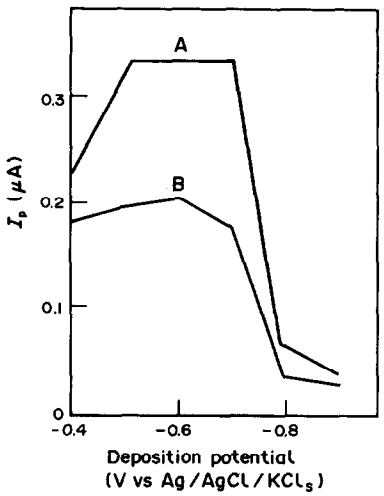

Figure 5
Influence of the deposition potential on the peak current. A, Piroxicam 1×10^{-7} M; B, Tenoxicam 1×10^{-7} M; H_2SO_4 0.05 M; t_{acc} = 60 s (from ref. 77).

The change of the peak height as a function of the deposition potential will indicate the optimum value. However, this choice may be subject to a compromise if interfering compounds are present in the sample.

It has been demonstrated that the reduced form of vitamin K_3 is more strongly adsorbed on the mercury drop electrode than the oxidized form. Owing to the reversibility of the quinone–hydroquinone couple, an accumulation of the reduced form and its subsequent oxidation will provide better sensitivity [16], but even in this case, the determination of the optimum deposition time remains of interest since the accumulated amount of material may vary to a large extent with this parameter.

The relationship between the amount of accumulated compound and the deposition time should be linear, indicating a constant adsorption rate. This increase will reach a maximum value rapidly at a rate depending on the solution concentration and the degree of saturation of the electrode surface. This linearity is not observed in some cases due to an equilibrium occurring between the adsorbed and dissolved species. This, often encountered, equilibrium, observed after the accumulation has been performed under stirring conditions, generally involves a rearrangement of the molecules after their adsorption at the electrode surface, in which a number of them are released [16]. This final state is immediately established in quiescent solution. This also means that when such a behaviour is observed, the influence of the equilibration time is to be controlled.

Linearity between the peak height and the concentration is generally observed between 10^{-7} and 10^{-9} M but, depending on the adsorption properties of the compound, this range can be extended from 10^{-6} to 10^{-10} M with detection limits of about 10^{-11} M. Higher detection limits are observed in complex media, mainly due to interfering compounds. At high concentrations, the curve deviates from linearity due to the saturation of the electrode surface. Since analytical measurements must be made using the linear part of the curve, such concentrations will be determined after dilution of the sample or by using shorter accumulation times or unstirred solutions.

Applications

Numerous applications of AdSV have been described but most of them are devoted to

the determination of the optimal working parameters for the determination of a given compound.

More than 200 organic compounds including a large number of pharmaceutical or biological substances and metal ions complexated with an organic ligand have been submitted to AdSV [17] (Table 3). In metal analysis, the working parameters have to be determined for each application, in particular the solution parameters which can affect the complexation reaction itself and the adsorption of the organometallic complex.

It is evident that the preferential accumulation of organic or inorganic analytes using modified electrodes represents an important application of the technique. Analytes can be concentrated by means of functional groups attached to the electrode surface or incorporated into a carbon paste matrix. The reactions involved include ion exchange, complexation or covalent bonding. The most commonly used anion exchanger is poly(4-vinylpyridine) which attracts anions due to its state of protonation [11]. Large, hydrophobic cations are preferably attracted by a cation exchanger, e.g. Nafion, which has been demonstrated to be useful in the determination of trace metals in body fluids [18] or for *in vivo* applications [19]. Dowex sulphonated polystyrene [20] and Amberlite [21] have been incorporated into a carbon paste electrode in order to preconcentrate copper and gold, respectively.

The immobilization or incorporation of a complexing reagent also allows the accumulation of several metal ions. Dimethylglyoxime has been mixed into a carbon paste electrode for nickel determination in complex media after a medium-exchange procedure [22, 23]. Other ligands have been utilized such as dithizone [24], alkyl-mercaptans [25], trioctylphosphine oxide [26] or 2,9-dimethyl-1,10-phenanthroline [27].

Combination of complexing ligands with ion exchangers has also been proposed. The introduction of dithiocarbamate into a conducting polypyrrole film has allowed the determination of copper ions [14, 28] while crown ethers have been used in association with Nafion to determine thallium, silver and lead [13]. The activity of dibenzo-18-crown-6-ether has been demonstrated by its selective uptake of lead ions from a solution containing copper, thallium and zinc ions at the same concentration level [29].

As previously mentioned, membranes have also been used to act as a barrier towards large sized molecules. Such a procedure has been proposed using a cellulose acetate membrane, for which the base hydrolysis results in uniform holes in the film. The size of the holes depends on the hydrolysis time [30, 31]. Applying this method, it has been demonstrated that a 2×10^{-8} M level of chlorpromazine or trimipramine can be determined without any interference from 120 mg l^{-1} of albumin or gelatin. Moreover, the chlorpromazine response is not affected by the bilirubin peak which overlaps when uncoated electrodes are used [32].

Table 3
Some organic ligands used for the determination of metal ions by adsorptive stripping voltammetry

Dimethylglyoxime	Ni, Co, Pd, Cr
Catechol	Cu, Fe, Sb, U, V
Solochrome Violet	Al, Ca, Mg, Sr, Ba, Ti
8-hydroxyquinoline	Cu, Cd, Pb, Mo, U
2,2′-bipyridine	Ni, Co
Eriochrome Black T	Mn
Mordant Blue	Th, U
Tropolone	Mo, Sn

A combination of this size-exclusion effect with ion exchanger or complexation modification may also improve selectivity. The association of hydrolysed cellulose acetate with Nafion enhances selectivity in metal ion analysis since cations of various size are attracted by Nafion while cellulose acetate film allows only the small cations to reach the electrode surface [33]. Another strategy to modify the carbon paste electrode is to incorporate microorganisms for the bioaccumulation and subsequent voltammetric reduction of metal ions. Algae, mainly *Eisenia bicyclis*, exhibits a preferential uptake of copper(II) ions under open circuit conditions, allowing their determination down to the micromolar concentration level with very high selectivity [34].

The application of the adsorptive stripping technique to biological molecules has permitted their quantitative determination (Table 4) and the investigation of interactions occurring between several proteins [35–37] and of the influence of the conformation of large sized molecules on their reactivity [38].

Among pharmaceuticals, several classes of compounds have been widely investigated (Table 4). Numerous benzodiazepines have been analysed since this group exhibits adsorption properties and the benzodiazepine azomethine bond is easily reduced. Some of the compounds have been determined in biological fluids. Flunitrazepam has been adsorbed in an open circuit at a bentonite — modified electrode from diluted samples of human serum and urine. It is possible to determine as little as 1.5 $\mu g\ ml^{-1}$ of sample [56]. Camazepam and bromazepam have also been analysed in human serum by using a HMDE. An extraction procedure is required in this case and detection limits of 20 and 200 ng per ml of serum were obtained for camazepam and bromazepam, respectively [51]. The dibenzodiazepine clozapine can be oxidized after its accumulation at a carbon electrode using an open circuit procedure. The glassy carbon electrode has a detection limit of 7.1 ng ml^{-1}, while a carbon paste electrode modified by incorporation of sepiolite has a detection limit of 34 ng ml^{-1}. However, only the latter electrode is able to accumulate selectively the dibenzodiazepine from human serum samples [74].

Among phenothiazine derivatives, promethazine, diethazine, trifluoperazine and fluphenazine have been collected through an adsorption–extraction process at a wax-impregnated graphite electrode. The determination of these tranquillizers in urine and plasma requires no preliminary treatment but the electrode has been covered with a Spectrapor membrane to prevent the fouling of the electrode by protein adsorption. This enhances sensitivity from 1×10^{-5} to 5×10^{-8} M using a 15 min accumulation time [62].

The oxidation of the tricyclic antidepressants imipramine, desipramine and trimipramine collected from urine samples at the surface of glassy carbon and carbon paste electrodes requires the transfer of the electrode to a blank solution to eliminate the interference by electroactive species. The carbon paste electrode also accumulates these compounds through an adsorption–extraction process [75].

Great attention has been paid to the determination of antitumour agents. Adriamycin can be adsorbed at a carbon paste electrode simply by immersing the electrode in the sample, rinsing it and placing it in a pH 4.5 buffer solution to perform the potential scan. This rapid analysis method, which requires <10 min, allows the determination of the drug in a urine sample from a cancer patient 2 h following intravenous administration [64].

Daunorubicin can be measured by its reduction or its oxidation using a HMDE or a carbon paste electrode, respectively. In this case, the analysis of a diluted urine sample requires no pretreatment when the mercury electrode is used while the carbon paste electrode requires a medium-exchange procedure and exhibits a lower sensitivity [67].

Table 4
Biological compounds and some groups of pharmaceutical compounds investigated by AdSV (with references)

Biological compounds	Benzodiazepines	Phenothiazines	Antitumour agents	Antibiotics
Adenine [39]	Bromazepam [51, 52]	Chlorpromazine [31, 58–61]	Adriamycin [63, 64]	Chlortetracycline [72]
Albumin [40]	Brotizolam [52]	Diethazine [62]	Chlorambucil [65]	Doxycycline [72]
Bilirubin [41]	Camazepam [51]	Fluphenazine [62]	Cisplatin [66]	Erythromycin [73]
Cytochrome *c* [42]	Chlorazepate [52]	Perphenazine [58]	Daunorubicin [67]	Novobiocin [73]
DNA [43, 44]	Chlordiazepoxide [53]	Phenothiazine [58]	Doxorubicin [63]	Oxytetracycline [72]
Folic acid [45, 46]	Clotiazepam [54]	Promethazine [62]	5-Fluorouracil [65]	Streptomycin [73]
Heme [47]	Diazepam [55]	Trifluoperazine [62]	Marcellomycin [14, 68]	Tetracycline [72]
Lipids [48]	Flunitrazepam [56]		Methotrexate [69, 70]	
Nucleic acids [43, 48, 49]	Medazepam [52]		Mytomycin [71]	
Uric acid [50]	Nitrazepam [55]			
	Prazepam [52]			
	Temazepam [57]			
	Triazolam [54]			

In another approach, a glassy carbon electrode covered with a negatively charged lipid layer has allowed the accumulation of marcellomycin from a diluted urine sample without the interference of uric acid which overlaps the anthracycline peak at uncoated electrodes. The accumulation step results both from electrostatic attraction and from the hydrophobic–lipophilic character of marcellomycin [68]. In order to increase the stability of the lipid layer, a new type of modified electrode is proposed by mixing the lipids into the carbon paste electrode [76].

It has been demonstrated that methotrexate can be directly determined in urine after a 1:4 dilution of the sample with the supporting electrolyte. The HMDE is used in this case but the determination in serum samples requires a preliminary extraction procedure [69].

5-Fluorouracil can be determined without the interference of uric or ascorbic acids, which often are present in biological samples. However, the presence of methotrexate gives considerable interference [65].

It appears from these examples that the HMDE gives lower detection limits than solid electrodes, even when complex media are analysed, and since it cannot be modified, a pretreatment of the sample is often required. On the other hand, the modification of solid electrodes avoids such pretreatments since several modifiers can be used to enhance selectivity by the size exclusion effect, preferential uptake or specific complexation. However these procedures result in lower sensitivity.

Adsorptive stripping voltammetry is useful in flow injection analysis with electrochemical detection. The deposition potential is imposed when the injected sample flows through the detector and the potential is scanned when the sample plug leaves the detector. In such cases, the accumulation time depends on the imposed flow rate. This procedure can be compared to the medium-exchange procedure since the stripping step is performed in an appropriate supporting electrolyte used as carrier. Moreover, in some cases involving the determination of strongly adsorbed analytes, the period during which the sample plug flows through the cell can be used as a washing period to eliminate some less adsorbed interfering substances.

Several compounds have been successfully determined using flow-through adsorptive stripping voltammetry, such as chlorpromazine in body fluids [58] and doxorubicin in urine [63].

Conclusion

Owing to the high sensitivity of the technique and the selectivity which can be obtained by modification of the working electrode, adsorptive stripping voltammetry appears to be very promising as it extends considerably the scope of applications of stripping analysis, even when complex media are investigated. It is beyond doubt that further developments and applications can be expected in the near future.

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