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2nd Edition
Volume II

Roger E. Schirmer

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Modern Methods of Pharmaceutical Analysis

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Editor

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INTRODUCTION

During the development of a new drug product, detailed chemical studies must be made of raw materials, synthetic intermediates, the drug substance itself, and the final formulated product. These studies must identify types and levels of impurities, degradation products, degradation rates, and analytical methods suitable for monitoring these factors. The information resulting from these studies is used to identify potential sources of safety problems in the product, to meet the requirements of foreign and domestic regulatory agencies, and as a basis for establishing quality control procedures and specifications for the product. The analytical effort required to provide this information can be divided into a number of tasks as shown in Table 1. The requirements for specificity, precision, accuracy, and the degree of complexity acceptable in the analytical procedure vary considerably from task to task and therefore require a variety of analytical techniques to satisfy them.

For example, the identification of impurities and degradation products requires the extensive use of chemical separations followed by qualitative analysis of the isolated product. Gas chromatography(GC) and high pressure liquid chromatography (HPLC) are frequently used to separate trace impurities, but older techniques such as thin layer chromatography (TLC), fractional crystallization, fractional distillation, and solvent extraction are still very important. However, the classical methods of identification by preparation and characterization of derivatives have been almost completely replaced by modern spectral methods of analysis. Elemental analysis, nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), and mass spectroscopy (MS) — especially GC/MS — are used almost exclusively for identification of unknown products.

In addition to identification of degradation products, it is necessary to measure the rates of degradation of the drug and its formulations under a variety of conditions. This information is needed to define conditions for storage and handling that will assure potency and safety throughout the expected shelf life of the product. Stability studies are especially demanding of analytical precision and accuracy because changes of a few percent over a period of 3 to 5 years are significant and must be accurately quantitated. In order to be able to detect such small changes reliably with a limited number of replicate assays at each time point, the analysis must be very precise, free of interference from the degradation products, and free of "drift" due to changes in instruments, standards, operators, etc. over a period of years. Gas chromatography, high pressure liquid chromatography, spectrophotometric, titrimetric, and electro-chemical methods are all capable of adequate precision. Regardless of the method of measurement, the procedure must be carefully designed to avoid chemical interferences and the method precision must be determined experimentally for use in designing the stability study.

The set of analytical procedures developed to control the quality of the final marketed product must include both qualitative and quantitative methods in order to assure the identity and purity of the product. Several categories of tests are usually included in a product specification and these are summarized in Table 2. All the procedures called out in the specification must be amenable to routine use in a quality control laboratory and must therefore be as simple and rapid as possible. The procedures used during product development can often be simplified without loss of essential specificity or accuracy because the real problems associated with the product have been defined by the developmental work. However, control limits on both the purity of the drug substance and the drug content of the finished formulation are usually very tight, thus requiring very precise quantitative procedures for testing compliance. The preferred solution to the problem of quantitative control assays is therefore to use HPLC or GC methods which afford simplicity, high speed, good specificity, and excellent precision and accuracy. An alternate that may be chosen when suitable GC or HPLC systems cannot be found, or for facilities where these instruments are not

readily available (a common problem in some foreign countries), is to combine a precise but nonspecific quantitative assay with a qualitative chromatographic test that shows the absence of interfering impurities. This approach is widely used in the compendia and in control procedures for older products. The quantitative analysis in these cases is often a titrimetric or spectrophotometric method, and the qualitative test a thin layer or paper chromatogram. Regardless of the methods chosen for the final measurement, quantitative analysis of formulated products almost always requires a preliminary separation of the drug from excipients. This separation is frequently accomplished by extraction, solvent partitioning, filtration, or column chromatography, but many other techniques find occasional application. In spite of the multiplicity of methods available, finding a reasonably simple procedure that gives a clean, quantitative separation of the drug from the excipients is often the most difficult step in development of procedures for analyzing formulations.

In many cases, quantitative analysis of drugs also requires the use of an analytical reference standard of well defined purity. A reference standard is required whenever a relative technique such as GC, HPLC, ultraviolet, visible or infrared spectrophotometry, fluorometry, or polarography is used for the analysis. Standards are also required for some qualitative tests such as identification by retention time, retention volume, or R_f value. The evaluation of the reference standard is accomplished using a series of tests similar to those listed in Table 2 for analysis of the drug substance. However, relative analytical techniques cannot be used to obtain a purity value because of their requirement for a reference standard (area normalization is used to estimate purity from GC and HPLC traces, but the values obtained must be treated as rough approximations to the true purity). The purity value of the standard must instead be derived from absolute methods, i.e., methods which do not require a standard of the same substance. The available absolute methods are titrations and gravimetric procedures (including methods used for elemental analysis), NMR, coulometry, differential scanning calorimetry, and phase solubility analysis. The requirement for reference standards in analyses with a wide spectrum of applications in pharmaceutical development and control makes the absolute methods especially important in modern pharmaceutical analysis.

The range of problems encountered in pharmaceutical analysis coupled with the importance of achieving the highest specificity, precision, and accuracy possible result in new techniques for organic analysis being adopted quickly in the pharmaceutical industry. The purpose of this book is to review several of the newer methods that now find wide application in pharmaceutical analysis, as well as several older methods (e.g., phase solubility analysis and ultraviolet/visible spectroscopy) of unique importance. The principle of each technique is discussed with emphasis on factors that directly affect its proper application to analytical problems. A thorough understanding of these principles is essential when selecting instruments, operating conditions, and sample preparation procedures to optimize the performance of an analysis, or when trying to identify the cause of a failure encountered in an existing procedure. Tabulations of data useful in method development and applications are also presented, including tables of characteristic ir, nmr, and uv band positions; composition of standard buffer solutions; properties of solvents; and properties of column packings for GC and HPLC. Finally, selected applications of each technique to problems in pharmaceutical analysis are reviewed. It is hoped that the broad coverage given each of the selected techniques will make *Modern Methods of Pharmaceutical Analysis* useful as a source of ideas and guidance in developing practical solutions to problems in pharmaceutical analysis.

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Table 1
ANALYTICAL TASKS IN DEVELOPMENT AND MARKETING OF A DRUG

Determination of identity and purity of starting materials and intermediates used in manufacturing the drug substance
Determination of the identity and purity of the drug substance
Isolation and identification of trace impurities in the drug substance
Determination of degradation rates and products for the drug substance
Determination of identity and purity of excipients used in manufacturing formulated products
Determination of degradation rates and products for the formulated drug
Establishment of an analytical reference standard for the drug substance

Table 2
OUTLINE OF QUALITY CONTROL TESTS FOR DRUG PRODUCTS

Identification Tests

Purpose: to confirm the identity of the principal component of a lot of raw material or formulation
Types of tests: color tests, melting points of the drug or derivative of the drug, formation of precipitates, ir or nmr spectrum, mass spectrum, X-ray powder pattern, chromatographic mobility, optical rotation, refractive index, density

Quantitative Analysis of the Drug Substance

Purpose: to determine the percent purity of the drug substance or the content of the active ingredient(s) in a formulation
Types of tests: *Absolute methods* — titrations, gravimetric procedures, differential scanning calorimetry, coulometry, nuclear magnetic resonance spectrometry, phase solubility analysis
Relative methods — gas chromatography, high pressure liquid chromatography, spectrometry (ultraviolet, visible, or infrared), fluorometry, polarography, microbiological assays

Tests for Specific Impurities

Purpose: to control the quantity of a specific impurity or group of inpurities in the drug product, such as water, solvents, metals, and trace organic impurities
Types of Tests: any test listed in Quantitative Analysis of the Drug Substance, atomic absorption, atomic emission, or semiquantitative limit tests using relative size of spots on thin layer chromatograms, spot tests with visual color comparison, etc.

Chromatographic Screen

Purpose: qualitative examination of the product for impurities, including contaminants not previously encountered
Types of tests: paper, thin layer, gas or high pressure liquid chromatography; electrophoresis; bioautography

Miscellaneous

Purpose: control of specific properties known to affect product performance or required by regulatory agencies
Types of tests: crystal form (X-ray or infrared spectroscopy), sterility, pyrogens, particle size, foreign matter, density, color, odor, etc.

THE EDITOR

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Chapter 1

POLAROGRAPHY

E. C. Rickard

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I. INTRODUCTION

Polarography is a generic term referring to several related voltammetric techniques which use the dropping mercury electrode (DME). The most well known is direct current (DC) or conventional polarography originally developed by Heyrovsky in 1922. However, the most successful developments in theory, instrumentation, and applications have been made within the last 10 to 20 years. This is particularly true for organic electrochemistry.[1-4]

The DME microelectrode consists of a mercury reservoir connected to a very small bore capillary tube upon which a mercury drop grows and drops every few seconds. The applied potential is slowly varied so that each drop is maintained at nearly constant potential, so that a complete polarogram will consist of current-time responses at many drops. Thus the current-potential behavior can be obtained over a wide range of potentials. According to the redox behavior of the species in solution, an electrolysis reaction will occur at some point in this potential scan. The electrolysis current is proportional to the concentration of the species in solution when material is transported to the electrode by diffusion. Thus a polarogram contains both qualitative and quantitative information. That is, the current-potential curve indicates both the nature and the concentration of the electroactive material present in solution.

The change in the area of the mercury drop and the nature of the diffusion process cause the current to alternately increase during the life of the drop and fall towards zero when the drop falls. If the current is measured only at a specific time during the life of the drop, usually at the point just before the mercury drop falls, the technique is called sampled DC polarography or Tast polarography. In addition to the characteristics imposed by the nature of the DME, DC polarography exhibits the following traits:

1. Polarography is essentially a comparative assay, requiring comparison of a sample response to a standard response.
2. Typical concentrations are millimolar. The useful concentration range is about 10 m*M* to 0.01 m*M*.
3. The required sample size is about 10 to 50 mℓ for conventional cells down to about 0.1 mℓ for microcells.
4. Selectivity is determined by the relative ease of oxidation or reduction of the individual components.

DC polarography can be applied to either reduction or oxidation processes. However, the mercury electrode itself is rather easily oxidized and limits the investigation of oxidation processes to those species which are more easily oxidized than the electrode. The very high overvoltage for hydrogen reduction on mercury makes the DME especially suitable for the investigation of reductive processes. Ultimately, the reduction properties of the sample solvent/supporting electrolyte determine the useful negative potential limit. Some of the electroactive species and functionalities which can be reduced are listed in Table 1; those which can be oxidized at the dropping mercury electrode are listed in Table 2.[5-9] It should be noted that polarography of inorganic species typically involves a change in the oxidation state of a central atom, usually a metal. On the other hand, electrochemical oxidation or reduction of organic compounds frequently involves changes in covalent bonds leading to interconversion of functional groups or substitution, addition, elimination, coupling, or cleavage reactions.[6]

Besides DC and sampled DC polarography, techniques which use the DME include pulse polarography, differential pulse polarography, alternating current (AC) polar-

Table 1
SPECIES AND FUNCTIONALITIES WHICH CAN BE REDUCED AT THE DME

Hydrogen ion and water
Higher oxidation states of many metals and their complexes
Inorganic oxidants such as bromate, iodate, chlorite, hypochlorite, hydrogen peroxide, and sulfur dioxide
Carbon-carbon bonds
  Aromatic hydrocarbons
  Alkenes
  Aryl alkynes
  Aromatic nitriles
Carbon-oxygen bonds
  Quinones
  Aldehydes
  Aromatic or other activated ketones
  Dicarboxylic acids
  Keto-acids
  Epoxides
Carbon-heteroatom bonds
  Imines (azomethine, $-C=N-$)
  Oximes ($-CO-C=N-$)
  Carbon-halogen (Cl, Br, or I)
  Nitriles ($-CN$)
  Hydrazones ($-C=N-NH_2$)
  Carbazones ($-N=N-CO-N=N-$)
Nitrogen-oxygen bonds
  Nitro ($-NO_2$)
  Nitroso ($-NO$)
  Hydroxylamine ($-NHOH$)
  N-oxide ($-N\rightarrow O$)
Sulfur containing compounds
  Disulfides ($RSSR'$)
  Sulfoxides ($-SO-$)
  Sulfones ($-SO_2-$)
  Thioethers (RSR')
Nitrogen, oxygen, and sulfur heterocyclic compounds
Others
  Azo ($-N=N-$)
  Azoxy ($-NO=N-$)
  Quaternary ammonium (R_4N^+)
  Peroxy ($ROOR'$)
  Organometallic

Table 2
SPECIES AND FUNCTIONALITIES WHICH CAN BE OXIDIZED AT THE DME

Lower oxidation states of some metals

Species which form insoluble mercury salts or strong mercury complexes such as halides, mercaptans (thiols), cyanide, azide, thiocyanide, and thiosulfate

Activated hydrocarbons, particularly condensed aromatics

Others
  Hydroquinones
  Dihydroxy or trihydroxy aromatics
  Hydroazo or hydrazines ($-NH-NH-$)
  Carbazides ($-NH-NH-CO-NH-NH-$)
  Ene-diols (such as ascorbic acid)
  Phenols
  Uracils
  Barbituric acids

ography, triangular sweep polarography (cathode-ray polarography), square wave polarography, radio frequency polarography, and various derivative and harmonic polarographic techniques. Several other voltammetric techniques which measure the current flowing through an electrolysis cell in response to an applied potential do not use a dropping mercury electrode. These include chronoamperometry, cyclic voltammetry (chronoamperometry with linear potential sweep), and stripping voltammetry which are performed at a stationary hanging mercury drop or a solid (platinum, graphite, etc.) electrode; hydrodynamic voltammetry which utilizes convective mass transfer to a stationary, solid electrode; and amperometric techniques which utilize convective transfer to a rotating (disk, ring-disk, or wire) or stirred (mercury pool) electrode. Amperometric titrations use the DME or other suitable electrode as the detector for a conventional titration when either the substance being titrated and/or the titrant and/or the product of the titration is electroactive. Differential pulse polarography, stripping voltammetry, and AC polarography are the most frequently used techniques for quantitation other than DC or sampled DC polarography. The characteristics and applicability of some of these related techniques will be discussed.[1,2,4,5,10-19]

This chapter will briefly present the fundamentals of polarographic techniques related to their use for quantitative analysis. Then, selection of variables such as electrolyte, cell, and instrumentation will be discussed. Finally, the application of polarography to analysis of selected compounds and group of compounds will be discussed. This chapter will not attempt to duplicate the many excellent reviews available for polarography. Instead, it will provide an overview and guide to more comprehensive reviews of specific aspects which may be of interest to readers. The frequently used symbols in this chapter are listed in Table 3.

II. ADVANTAGES AND LIMITATIONS

In comparison with other analytical techniques, DC polarography has several advantages and disadvantages.[2,4,9-11,14,20-24] One of the well known advantages of electrochemical techniques which employ the DME is its reproducible, constantly renewed surface. Any contamination of the electrode surface or accumulation of insoluble electrolysis products is removed by the fall of the old drop and the formation of a new drop. Also, only one drop is affected by any temporary disturbance of the diffusion process (such as vibration) whereas the entire voltammetric experiment would be affected at a stationary electrode. Some of the other advantages are listed below.

1. Polarography is applicable to a wide variety of reducible and oxidizable functionalities as described above.
2. The precision is good, typically about 1 to 2% for concentrations greater than about $10^{-4}M$.
3. The sensitivity is high, with a detection limit of about $10^{-6}M$ (0.1 μg/mℓ for a molecular weight of 100). It can be extended to about $10^{-8}M$ (1 ng/mℓ for a molecular weight of 100) using differential pulse polarography or about $10^{-9}M$ for stripping voltammetry (generally limited to metals and a few anions). This compares to typical sensitivity ranges of about 1% (in sample) for infrared spectroscopy; mg/mℓ for nuclear magnetic resonance spectroscopy; mg/mℓ to μg/mℓ for high pressure liquid chromatography; μg/mℓ for UV spectroscopy, gas chromatography-mass spectroscopy (total ion current) or gas chromatography (FID detector); μg/mℓ to nanogram/mℓ for fluorescence spectroscopy, atomic absorption spectroscopy or gas chromatography-mass spectroscopy (single or multiple ion detection), and nanogram/mℓ for gas chromatograpby (EC detector) or flame emission spectroscopy (alkali or alkaline earth elements).[25]

Table 3
DEFINITION OF SYMBOLS

Symbol	Definition
A	Electrode area, cm^2
a	Area of adsorbed molecule, $Å^2$
B	Adsorption coefficient, cm^3/mole
C*	Bulk solution concentration, m*M*
C_i	Concentration of i'th species, m*M*
C_s	Concentration of standard
C_u	Concentration of unknown
D_i	Diffusion coefficient of i'th species, cm^2/sec
d	Density of mercury, 13.534 g/cm^3 at 25°C
E	Electrode potential, V
E^o	Standard electrode potential, V
$E'_{1/2}$	DC polarographic half-wave potential of the i'th species, V
E_p	Peak potential, differential pulse polarography and cyclic voltammetry, V
ΔE	Pulse height, differential pulse polarography, or peak-to-peak applied AC voltage, AC polarography, V
E_{DC}	DC potential of applied signal in AC polarography
E_{pzc}	Potential of zero charge on the DME, V
E_r	Potential at which scan direction is reversed in cyclic voltammetry, V
E_i	Initial potential before application of pulse (pulse polarography or differential pulse polarography) or start of scan (cyclic voltammetry), V
E_2	Final potential after application of pulse, pulse polarography, V
F	Faraday's constant, 96487 c/eq
f_i	Molar activity coefficient of i'th species
h_{corr}	Corrected mercury column height, cm of mercury
I	Diffusion current constant in DC polarography, $\mu a\ sec^{1/2}\ mM^{-1}\ mg^{-2/3}$
I(ωt)	AC current in AC polarography, μa
$I_{p,AC}$	Peak current in AC polarography, μa
$\bar{i}$	Instantaneous current, μa
$\bar{i}$	Average current over the drop life, μa
i_d	Diffusion limited current, DC polarography, μa
i_c	Charging current, μa
i_k	Kinetic current, CE mechanism, μa
$\bar{i}_{cat}$	Average current, catalytic regeneration mechanism, μa
i_{ads}	Limiting current for adsorption pre-wave, μa
i_{pp}	Diffusion limited current, pulse polarography, μA
Δi_{DPP}	Current, differential pulse polarography, μA
Δi_{max}	Diffusion limited maximum current, differential pulse polarography, μA
i_L	Limiting current, voltammetry at RDE, μA
i_p	Peak current, cyclic voltammetry, μA
i_{corr}	Diffusion limited current corrected for dilution, μA
K_d	Dissociation constant for metallic complex
K_{eq}	Equilibrium constant for a chemical reaction
K'_{eq}	Pseudo-first-order equilibrium constant
k_i	Rate constant of i'th chemical reaction
k'_i	Pseudo-first-order rate constant
k_f and k_b	Forward and reverse heterogeneous electron-transfer rate constants, cm/sec
k_s	Standard heterogeneous electron-transfer rate constant, cm/sec
m,	Mercury flow rate, mg/sec
n or n_i	Number of electrons transferred in an electrode reaction
n_a	Number of electrons transferred in the rate controlling step of an electrode reaction
Q	Charge, μC
q	Stoichiometric coefficient of species
R	Gas constant, 8.314 Joule/(°K-mole)
(RT/F)	ln(10) 0.05915 at 25°C
r	Drop radius, cm

Table 3 (continued)
DEFINITION OF SYMBOLS

Symbol	Definition
T	Absolute temperature, °K
t	Time, sec
t_{const}	Drop time of controlled drop time DME, sec
t_a	Length of time required to reach adsorption equilibrium in pulse polarography, sec
t_1	Time interval from start of drop to current measurement, pulse polarography and differential pulse polarography, sec
t_2	Time interval from application of pulse to current measurement, pulse polarography and differential pulse polarography, sec
t_3	Time interval from start of drop to first current measurement, differential pulse polarography, sec
t_+	Transport number of cation
V	Volume of standard, standard addition, mℓ
v	Volume of sample, standard addition, mℓ
x	Distance from electrode, cm
y	Kinetic parameter, rate-controlled electron transfer and CE mechanisms
z_i	Ionic charge of i'th species
A, I, M, Ox, O, O_i, Red, R, R_i, X and Z	Symbols for chemical species involved in electrolysis mechanisms
α	Electron transfer coefficient
Γ	Amount of material adsorbed on electrode (surface excess), moles/cm²
Γ_m	Maximum amount of material which can be adsorbed on electrode, moles/cm²
Θ	Ratio of equilibrium concentrations of oxidized and reduced species at the electrode surface
$\varkappa$	Integral capacitance, μF/cm²
λ_i	Equivalent ionic conductivity of the i'th species
μ	Ionic strength, *M*
ν	Scan rate, cyclic voltammetry, V/sec, or kinematic viscosity, cm²/sec
ω	Angular frequency, radians/sec

4. The linear dynamic range is large, about 10^3 for high precision work with DC polarography, up to 10^6 including differential pulse polarography.
5. The instrumentation is very simple and relatively inexpensive. Both commercial units and circuit descriptions for construction of instrumentation are readily available.
6. Aqueous supporting electrolytes are commonly used for routine assays. However, many nonaqueous or mixed solvents may be used when greater sample solubility is needed.[26-28]
7. Relatively little sample preparation is usually necessary, even in the case of formulations.[5] Polarography is applicable to control assays of raw material drug substances or formulations, stability or dissolution studies and assays of drugs in biological fluids.[23]
8. The analysis time is relatively fast, typically about 15 to 30 min per sample, and the analysis is easily automated.[29-31]
9. The amount of sample actually electrolyzed is very small, less than 0.05 mℓ for reasonable electrolysis times. Thus, multiple polarograms can be obtained without altering the solution composition (for sample volumes greater than a few milliliters) and/or the sample may be recovered after analysis.

Some of the limitations of DC polarography include:

1. Current oscillations and charging current due to the constantly changing electrode area add complexity and limit sensitivity.
2. The technique is not as well known or frequently applied as many other instrumental techniques.
3. Although the relative ease of reduction or oxidation imparts some selectivity (more than many titrimetric techniques, for example), it is much less selective than most chromatographic or spectroscopic techniques.
4. Commercial instrumentation for automated analysis is just now becoming available. Like other instrumental techniques, optimal design of digital and microprocessor controlled instrumentation is still in a developmental state.
5. Electrode processes are frequently complex and difficult to understand. This problem is alleviated somewhat by the numerous investigations of model compounds and by careful characterization (during assay development) of factors which may affect the analytical application.
6. It is difficult to investigate oxidation processes due to the ease of oxidation of the mercury electrode. However, oxidation processes can be investigated with other voltammetric techniques and electrode materials.

III. PRINCIPLE

Electrochemical techniques are concerned with the interrelationships of potential (voltage), current or charge, and time.[19] Potentiometry is a static or zero current measurement of electrode potential in response to solution composition such as the measurement of pH. Measurements of conductance or dielectric constants are other zero current techniques. Dynamic electrochemical techniques (nonzero current) consist of controlled potential (voltammetric), controlled current, and controlled charge techniques. As previously stated, polarography is a voltammetric technique based on the measurement of current flowing through a dropping mercury electrode in response to the applied potential.

A. Description of Experiment

The basic polarographic experiment is illustrated in Figure 1. That is, the DME and a second electrode (required to complete the electric circuit) are placed into the electrolysis cell containing the solution to be analyzed, perhaps a 1 m*M* solution of cadmium ions. The potential difference between the DME and the other electrode is varied while the resulting current flow is measured. If the second electrode has a fixed potential (i.e., it is a reference or nonpolarized electrode such as a saturated calomel electrode), the relative potential of the DME can be measured. When the potential initially applied to the DME is sufficiently positive, the electrode and solution will be in equilibrium and no current will flow. If the potential applied to the DME is then scanned negatively, a value will be reached where the cadmium ions near the electrode will no longer be in thermodynamic equilibrium with the electrode. That is, some of the cadmium ions will be reduced to metallic cadmium. Since the metallic cadmium is soluble in mercury but not in the solution, the reduced cadmium will remain at the electrode in the form of cadmium amalgam. In other cases, the electrolysis product might remain in solution or on the electrode surface. As the DME is made even more negative, all the cadmium ions which arrive at the electrode surface will be reduced. The limiting current which results is proportional to the concentration of the electroactive species when diffusion is the mass transfer process which brings material to the electrode. The applied potential function and the resulting polarogram (current-potential plot) are

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