UNCOMPLIANT DRUGS AS INHIBITORS IN ELECTROCHEMICAL PROCESSES

PhD Thesis – Summary

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The PhD thesis has been developed as part of the PhD program at the University Politehnica Timisoara, Laboratory of Electrochemistry, Corrosion and Electrochemical Technologies at Department of Applied Chemistry and Engineering of Inorganic Compounds and Environment.

The proposed research topic aims to **valorize the active substances from uncompliant drugs** (expired, counterfeit, qualitatively inadequate) as additives in copper and nickel galvanic electrodeposition baths and as corrosion inhibitors for steel, copper and nickel in acidic environments.

Due to the currently large amounts of expired drugs [1,2], as well as the neutralization techniques, which are polluting [3-6], there is an increased interest in recycling and/or reusing them in other processes.

Uncompliant drugs are currently disposed is through incineration, polluting thus the atmosphere. Another part of these, which are not sent to incineration centers and are stored improperly, accumulate in wastewater or soil [1-6], having a negative impact on the environment.

Since most active substances in drugs are more expensive than most frequent additives used, our attention has been focused on expired drugs. The use of active substances from expired drugs has two major benefits: limiting environmental pollution with active pharmaceutical compounds and reducing waste disposal costs. On one hand, even small amounts of drugs released into the environment represent a major risk for both aquatic and terrestrial ecosystems [7,8]. On the other hand, expired drugs neutralization is generally done by incineration and therefore represents a danger for waste elimination in the environment.

The general objective of this thesis is the study of the possibilities of recycling uncompliant drugs as leveling agents in the electrodeposition processes of copper and nickel, and as corrosion inhibitors for steel, copper, and nickel, to valorize them after the expiration date and reduce neutralization costs, as well as decrease the polluting emissions produced from their incineration. To achieve the general objective, the following **specific objectives** have been proposed:

- Studies on the possibilities to use the active substances from expired drugs as leveling agents in acidic galvanic baths for copper and nickel deposition;
- Studies on the possibilities to use expired drugs as corrosion inhibitors for different metals in certain aggressive environments (carbon steel, copper and nickel in acid solutions);
- Molecular modeling studies on the correlations between the structure of organic compounds existing as active substances in expired drugs and the possibility to use them as inhibitors in different environments;
- Identification of the action mechanisms of these compounds in the electrodeposition

processes;

- Clarification of the action mechanism of active substances from uncompliant drugs studied on the inhibitory effect on the corrosion process;
- Studies of the electrochemical behavior and stability of different drugs used in the thesis, in a wide range of potentials, in different acid electrolytic environments:
- Elucidation of the expired drugs adsorption mechanisms on the active metal surface, in galvanization or corrosion processes, using adsorption isotherms;
- Demonstrating the leveling capacity of expired drugs in nickel and copper electrodeposition, as well as the inhibitory efficiency on metals corrosion in acid solutions.

Experimental studies have been carried out in **two directions of reuse of expired drugs**. First research direction approached is the use of active substances from **expired drugs as additives** (leveling agents) in the copper and nickel electrodeposition, and the second consists in using them as **inhibitors for the corrosion** processes of carbon steel, copper and nickel.

The research topic idea approached started from the **similarity of structural elements** present in the molecules of classic, **commercial inhibitors** currently used and the **active substances present in some drugs**. It was sought that the molecules of the active substances used have structures that can perform physical or chemical interactions with metal atoms: aromatic rings, π electrons from multiple bonds, O, S or N heteroatoms, which contain pairs of non-participating electrons.

The theory underlining the experimental studies, the action mechanisms of inhibitors and a literature study on the use of active compounds from drugs as inhibitors are presented in **chapters 1-3**.

The goals of the electrodeposition-based industrial branch are varied, from obtaining objects with high aesthetic and commercial qualities [9], to increasing the corrosion resistance of the metallic substrate through coating with a thin layer of a more noble metal [10].

The **metallic layer quality** obtained through galvanization is determined by the crystalline structure of the deposit. The parameters defining the structure of a metallic layer are the size and orientation of the crystals, which are portions of a crystalline substance in which the particles form an ordered structure.

The crystal growth rate can be controlled either by the charge transfer carried out on the cathode surface or by the diffusion of metal cations towards the electrode. The crystal growth rate has a significant influence on the morphology and macroscopic structure of the deposits: in diffusive control, coarse metallic deposits are obtained, frequently with the unfavorable effect of dendrites appearing on the cathode surface, while in activation control, the deposits are optimally qualitatively, having a flat shape and uniformly consolidated layers [11].

Obtaining a compact, smooth and adhesive metal deposit requires the fulfillment of the following conditions: relatively high density of crystallization nuclei, a stage of charge transfer with a moderate overpotential, high crystallization overpotential values. According to the current theories, the additive adsorption on the protrusions causes a local inhibition of the electrocrystallization [12,13].

A characteristic of leveling and/or brightening additives used in the galvanic baths is the granulation reduction of the electrodeposited metallic layers. The dimensions of the metal granules depend on factors that describe the electrocrystallization stage: nucleation - the formation of a certain number of crystallization centers and their growth (the number of dislocation generators for the growth of the formed crystals). Obtaining microcrystalline cathodic layers characterized morphologically by a fine granulation depends on a high density of nucleation centers and implicitly, on all factors influencing the number of nucleation centers, such as: overpotential, cathodic current density, impurities in the electrolyte solution and additives adsorbed on the cathode surface [12,13].

During the metal deposition process, additives in the galvanic baths decrease their concentration in the electrolyte solution because they are consumed through incorporation into the metal deposit formed on the surface of the plated metal (adsorption process) or by an electrochemical reaction occurring at the electrodes [14,15]. The inhibitory effect of additives results in the need for an energy surplus for the formation of the deposit, with the consequence of decreasing the value of the electrolysis current at a constant potential or increasing the overpotential at a constant current. The increase in cathodic polarization is more pronounced than the decrease in faradic efficiency, caused by the reduction of additives or the more pronounced inhibition of discharge and metal deposition than the concurrent cathodic reaction - hydrogen evolution, effect observed on the polarization curves [16].

The additives effect on the overall process of electrodeposition is mainly due to the adsorption on the active surface of the electrode of their molecules or the compounds resulting from partial reduction. The bonds formed between these compounds and the metal support are strong (chemosorption), made between the π electrons of the unsaturated groups present in the additive molecules and the cathode. However, at the electrode, the adsorption of additives is competed by the adsorption of other species: water molecules, anions, metal cations, etc., and the surface of the support on which these processes take place is dynamic because of the continuous evolution of the electrocrystallization stage [17].

In the case of a simple, one-electron charge transfer process, both the activation energy of the specific elementary steps and the kinetic parameters, the exchange current density i_o and the cathodic charge transfer coefficient ($1-\alpha$) will be modified. If the cathodic process is more complex, involving a charge transfer in multiple successive stages, the additives used can also have a complementary role to the primary one, partially blocking certain areas of the active surface or the already deposited layer, modifying the kinetic parameters of other component stages of the cathodic reaction [18].

It can be stated that the additive molecules present in the galvanic baths can influence any of the stages of the global process of metal electrodepositing: the transport of metal cations to the electrode, the charge transfer, or the electrocrystallization reaction.

Additives in galvanic baths can be transported to the cathode interface by electrosorption, a theory supported by the fact that concentration of these substances in the electrolyte solution is much lower than the concentration of the metal ions. To define the mechanism by which these surfactant compounds favor electrosorption, although experimental studies do not indicate a direct dependence between leveling capacity and the brightening degree of the metal deposit and the additives surfactant properties, other properties are also necessary to be involved in this relationship [9].

If the additives are aromatic organic compounds, the electrosorptive effects are attributed to interactions between π electrons of the benzene nucleus and the supporting metal, including partial charge transfer between the two components at the electrochemical double layer level. This charge transfer is dependent on the energy required for electron extraction, the ionization potential, and the affinity for the electrons of the adsorbent [9,17].

In most specific cases of galvanic practice, the two types of electrosorption, structure sensitive and current density sensitive, either act together or interfere.

Up to this point, **there is no theory explaining in a unified way all the effects of additives in galvanic baths** with leveling and brightening properties, due to the difficulties that converge from the additives mechanism of action that is not unique, can vary during electrodeposition depending on the electrode area, the process moment, working conditions and, especially, the metal and electrolyte used.

In terms of **metal corrosion**, the damage caused by corrosion is enormous. According to estimates made by NACE International (National Association of Corrosion Engineers), the highest authority in the field, the global cost of corrosion of metals and alloys is estimated at 2.5 billions dollars/year, representing 3.4% of the world's gross product, in the conditions that corrosion protection measures are applied [18].

In principle, corrosion of metals and alloys in aqueous environments occurs through an **electrochemical mechanism** consisting of **two parallel electrode processes**: the **anodic ionization of the metal** and a **cathodic process in which the excess electrons resulting from the metal entering the solution as ions are consumed**. The susceptibility to corrosion of metals depends on the environment *pH* and the potential established at the metal/solution interface. To delimit the potential and *pH* domains in which a metal or alloy is thermodynamically stable, Marcel Pourbaix proposed the use of potential-*pH* diagrams (thermodynamic stability diagrams), known as Pourbaix diagrams [19]. Another way of protection against corrosion is based on the influence on the kinetics of the process, by limiting the rate at which the anodic and/or cathodic process takes place. Corrosion inhibitors are used for this purpose.

A significant category of **inhibitors** is represented by **organic compounds that could adsorb on the metal surface**, thus blocking the diffusion of the participating particles (reactants and reaction products) in the overall corrosion process. Such compounds are known as adsorption inhibitors. The most efficient organic compounds as corrosion inhibitors are those containing heteroatoms with non-participating electron pairs (N, P, S, O) or multiple C-C bonds in their molecule [20].

An important role is occupied by organic compounds with nitrogen: primary, secondary, tertiary amines, diamines, and quaternary ammonium salts [21]. Another class of heterocyclic nitrogen inhibitors is represented by triazines (1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine), which contain three nitrogen heteroatoms in their molecule, therefore, they have three pairs of non-participating electrons available for nucleophilic interactions. The inhibitory effect is accentuated if the hydrogen atoms in the triazine molecule are replaced with large hydrophobic groups.

Heterocyclic compounds with sulfur have also been the subject of numerous studies in which the inhibition effect for corrosion of metals in aqueous solutions has been revealed. The ability of such combinations to adsorb at the metal/aqueous solution interface is primarily due to the presence of the two non-participating electron pairs of the sulfur atom.

To avoid the use of toxic compounds as corrosion inhibitors, a series of amino acids and their derivatives have been tested. Their action is due to the presence of carboxyl and amino functional groups in their molecule [22].

Legislative restrictions on the use of toxic and hazardous substances have oriented research on corrosion inhibitors towards environmentally friendly substances. The concept of green corrosion inhibitors has emerged. This category includes substances, usually natural or like natural, that meet standards regarding toxicity, biodegradability and bioaccumulation [23]. Research in this field, which began with the study of natural extracts from plants (roots, bark, flowers, fruits, seeds), has been encouraged by the abundance of natural resources. Several compounds with inhibitory effect on the processes occurring on the surface of metals in contact with an aqueous solution have been identified in natural extracts: polyphenols, alkaloids, tannins, flavonoids, ascorbic acid, sorbitol, methionine, maleic acid, glycosides, caffeine, proteins, amino-acids, theophylline, coumarin and others [24].

Continuing the identification of green inhibitors, the attention of researchers was focused on the use of active substances in drugs, given that most of them contain in their molecules structural elements that favor the adsorption process at the metal/aqueous solution interface. Among the first drugs studied in terms of inhibitory properties in corrosion processes are antibiotics, such as ampicillin, cloxacillin, flucloxacillin and amoxicillin, whose inhibitory efficiency reached up to 90% [25].

The main reason for starting the **study of active substances in drugs** was that **in their molecules are structures that can form physical or chemical interactions with metal atoms**: aromatic rings, π electrons from multiple bonds, heteroatoms of O, S or N, which contain non-participating electron pairs [26].

On the other hand, the study of expired drugs as inhibitors was stimulated by the US FDA, which reported the maintenance of drug properties for a long time after the expiration date for 90% of the reserve stock of the US army.

Our attention was directed towards **the use of active substances from expired drugs**, as it is an **accessible and inexpensive alternative to replace commercial inhibitors**.

The experimental studies carried out to identify alternatives for the use of expired drugs has as starting point **chapter 4**, in which the materials, equipment and experimental techniques used are described.

Chapter 5 presents studies on the possibility to use expired drugs as **additives in the electrodeposition process of copper and nickel from acidic baths**. Experiments were carried out on two antibiotics from the cephalosporin group, **ceftazidime** (CZ) (the active substance in drug **Ceftamil®**) and **ceftriaxone** (CX) (the active substance in **Cefort®**) [27-29]. There are no studies in the literature data about using drugs as additives in electroplating.

The experimental determinations began with the electrochemical behavior study of the two active substances from drugs in acid electrolyte solutions, similar to those industrially used, without metal ions content.

It has been found that in strong acid medium (H_2SO_4), CZ does not undergo electrochemical transformations, while in weak acid medium (H_3BO_3), at advanced anodic polarization, it oxidizes to different compounds. As for the behavior of CX, in strong acid medium, in addition to the characteristic peaks of the curve plotted on the Pt/H_2SO_4 electrode, at potential values more positive than +1.00 V, an oxidation plateau associated with the oxidation of CX to different reaction products is observed. In weak acid medium, no additional peaks are distinguished from the characteristic base curve, so it can be stated CX does not undergo electrochemical transformations in the studied potential range.

In addition, it has been observed that the electrode processes (HER and OER) is inhibited with the increase of CZ and CX concentrations added to the electrolyte solutions.

It can be said CZ and CX can be used in both baths, as the anodic polarization does not exceed these potential values to oxidize the organic compounds during the metals galvanizing.

The study continued with the influence of organic compounds addition on the processes in electrolyte solutions containing 5 g L^{-1} metallic ions, Cu^{2+} in 0.5 mol L^{-1} H_2SO_4 for copper electroplating bath, and Ni^{2+} in 30 g L^{-1} H_3BO_3 for nickel one. Linear voltammetry (LV) curves have been plotted, from which, based on the corresponding Tafel plots, the kinetic parameters characteristic of the processes (exchange current density i_o and the cathodic charge transfer coefficient $(1-\alpha)$) were calculated. Knowing the exchange current density values, the activation energy was determined from Arrhenius diagrams.

From electrochemical impedance spectroscopy (EIS) measurements, the charge transfer resistance R_{ct} and double-layer capacity C_{dl}, necessary for characterizing the processes that take place at the metal/electrolyte solution interface, were calculated. From the R_{ct} values obtained without and with inhibitors, the surface coverage degree θ was estimated. Based on the values of the surface coverage degree, Langmuir adsorption isotherms were plotted, from which the Gibbs free energy of adsorption was calculated, which gives us information about the nature of interactions between the electrode and the organic additive present in the electrolyte solutions.

LV studies have shown that CZ and CX act as inhibitors on the studied processes, the characteristic overpotentials of copper and nickel electrodeposition being shifted to more negative values, proportional to the amount of organic compound introduced into the electrolyte solution. Kinetic parameters characteristic to the cathodic deposition processes are also influenced by the presence of the organic compounds in the electrolyte solution. According to the Butler-Volmer relationship, the addition of CZ and CX produces an inhibition phenomenon, modifying the kinetic parameters of the processes in the sense that the net current density passing through the interface is decreased, that is, the process is inhibited. At a temperature of 25°C, the exchange current density decreases by 4 to 5 orders of magnitude with the addition of the maximum inhibitor concentration in the case of nickel deposition. A similar, but less pronounced effect is observed in the case of copper electrodeposition. Increasing the temperature involves increasing the exchange current density, as the blocking effect of active sites on the electrode surface with inhibitor is counteracted by the increase of thermal agitation, thus reducing the activation energy of the electrodeposition process. Also, the apparent activation energy E_a values obtained from Arrhenius diagrams confirm the inhibitory effect of CZ and CX, E_a increasing with the increase of inhibitor concentration into the electrolyte solution.

EIS data provided additional information about the mechanism of copper and nickel electrodeposition. From the shape of the Nyquist spectra, it can be stated nickel deposition is controlled only by the charge transfer stage, while copper deposition is controlled by both charge transfer and mass transport. The results of the equivalent electric circuit modeling have revealed the strong influence of the organic compound addition on the studied processes. Regardless of the discussed process, at the same potential value, it was found that the charge transfer resistance increased when CZ or CX was added into the electrolyte solution and decreased with increasing the polarization.

The electrode coverage degree with adsorbed organic molecules increases with the addition of organic compounds in the electrolyte solution, obtaining high values at the maximum added concentration, up to 0.9 in the case of nickel deposition and 0.5 in the case of copper one with 10^{-3} mol L^{-1} CZ adition.

Values close to -40 kJ mol^{-1} of Gibbs free energy of adsorption suggest a chemical adsorption of CZ and CX on the metallic electrode surface.

Next, copper and nickel deposits were plated from galvanic baths with similar compositions to those industrially used: 0.5 mol L^{-1} H_2SO_4 + 250 g L^{-1} $CuSO_4 \cdot 5H_2O$, for copper electrodeposition, and 300 g L^{-1} $NiSO_4 \cdot 7H_20$ + 45 g L^{-1} $NiCl_2 \cdot 6H_2O$ + 30 g L^{-1} H_3BO_3, for nickel electrodeposition, in which different concentrations of expired drugs were introduced. The morphology of the layers obtained without and with CZ and CX was compared. It was found that even small amounts of drugs (10^{-4} mol L^{-1} active substance) added to the electrolyte solution have a leveling effect on the electrodeposited copper and nickel layers, resulting in fine, compact layers with smaller granulation.

Finally, the experimental results were verified through molecular modeling studies of CZ and CX molecules in aqueous environment. These confirmed the interactions between the inhibitors (CZ and CX) and metal (Cu and Ni) are of a chemical nature.

There are numerous literature studies regarding the alternative use of medications as corrosion inhibitors. In **chapter 6**, the experimental results obtained on the use of expired drugs as corrosion inhibitors are shown. Studies on the influence of **midazolam** (MID) (the active substance in **Midazolam Torrex**) on the **corrosion of copper in nitric acid solution** (Chapter 6.1), **paracetamo**l (PCM) (the active substance in **Perfalgan®**) on the **corrosion of OL52-3k carbon steel** (Chapter 6.2) and **ceftriaxone** (CX) (the active substance in **Cefort®**) on the **corrosion of nickel** in **sulfuric acid** and **hydrochloric acid** solutions (Chapter 6.3) are presented [30-32].

Based on the experimental results obtained, Midazolam Torrex drug proved to be an effective inhibitor for copper corrosion in 0.1 mol L^{-1} HNO_3 solution, reaching a maximum inhibition efficiency of 92.9% (gravimetric method, potentiodynamic polarization) for a concentration of 10^{-4} mol L^{-1} MID.

The results obtained from the potentiodynamic polarization curves showed that MID is a mixed-type inhibitor, acting preferentially on the cathodic process. The mechanism of inhibition determined from thermodynamic calculation was chemosorption, following the Langmuir adsorption isotherm model.

EIS measurements showed that MID addition to the corrosive test solutions lead to improving considerably the corrosion resistance of copper, as indicated by the increased charge transfer and diffusion resistances. Another aspect highlighted by EIS measurements is the decrease of the double-layer capacity, an effect due to the adsorption of MID molecules on the copper electrode surface by replacing the previously adsorbed water molecules, which displace the inner Helmholtz plane from the metal surface.

Scanning electron microscopy analysis indicates the inhibitory properties depend on the inhibitor concentration added into the acid solution, a high degree of protection at the maximum concentration of 10^{-4} mol L^{-1} MID being obtained.

The quantum chemical parameters evaluated clearly indicate a high tendency of MID to transfer electrons to the vacant d orbitals of copper, forming chemical bonds, which explains the appearance of a protective inhibitory film on the metallic copper surface in the aggressive environment studied.

The MID molecules adsorb on the copper surface by transferring electrons from MID to the low-energy vacant d orbitals of copper. The formation of such donor-acceptor complex bonds between the free electrons of the inhibitor and the vacant d orbitals of the metal is responsible for slowing down or stopping the corrosion process.

Studies on the possibility of using PCM as an inhibitor for OL52-3k carbon steel corrosion process in sulfuric and hydrochloric acids had the electrochemical behavior of PCM in the corrosive solutions as starting point.

It was found that in 0.5 mol L^{-1} H_2SO_4 solution, PCM undergoes an electrochemical quasi-reversible oxidation process in two steps. In 1 mol L^{-1} HCl solution, this compound is stable throughout the range of potential studied. PCM and its oxidation products have an inhibitory effect on the electrode processes, due to the adsorption of organic molecules on the electrode surface.

The concentration of PCM added in the acid environments significantly affects the corrosion rate of OL52-3k samples, and the inhibitory efficiency. Parameters calculated by potentiodynamic polarization, confirmed by the EIS results, support the decrease in corrosion rate and increase in inhibitory efficiency with increasing the concentration of PCM added in the electrolyte solutions, achieving a maximum inhibitory efficiency at the addition of 10^{-3} mol L^{-1} PCM, 96% in 0.5 mol L^{-1} H_2SO_4 solution and 85% in 1 mol L^{-1} HCl solution.

Thermodynamic parameters for PCM adsorption on OL52-3k electrode in 0.5 mol L^{-1} H_2SO_4 and 1 mol L^{-1} HCl solutions, obtained based on Langmuir isotherm model suggest a chemical interaction between the metal and the inhibitor molecules.

Chronoamperometric data confirmed the reaction mechanism, the current density values decreasing with the increase of PCM concentration added in the electrolyte solution, due to the blocking effect of the electrode surface corrosion sites with adsorbed organic molecules and the formation of a protective barrier, following the results model obtained by potentiodynamic polarization and EIS.

Studies of PCM molecular modeling in aqueous environment have confirmed that the bonds formed at the PCM/metal interface are of chemical nature.

The possibility of using CX as an inhibitor for nickel corrosion in acidic corrosive environments (0.5 mol L^{-1} H_2SO_4 and 1 mol L^{-1} HCl) was investigated next. In the experimental studies, different concentrations of CX, between 10^{-6} and 10^{-3} mol L^{-1}, have been used to determine the electrochemical behavior of CX in the test solutions.

It was found that in sulfuric acid, in the potential range of +1.35 to +1.65 V, CX is oxidized to different reaction products. In hydrochloric acid, CX is stable throughout the studied potential.

The values of inhibition efficiency, estimated by the gravimetric method, potentiodynamic polarization method and electrochemical impedance spectroscopy, were comparable, reaching a maximum value of 78% at the addition of 10^{-4} mol L^{-1} CX in sulfuric acid, and 73.9% at the addition of 10^{-5} mol L^{-1} CX in hydrochloric acid. A higher concentration of expired drug favors nickel complexation reaction with CX and thus increasing the corrosion rate, a fact noted especially at the maximum concentration used, 10^{-3} mol L^{-1}.

The decrease in the corrosion rate of nickel in the presence of CX and/or its oxidation products can be attributed to the adsorption of the organic compound on the metal surface, blocking the active sites produced by corrosion.

Morphological analysis of the corroded samples surface in the absence and presence of different concentrations of CX used in the experimental studies confirms the results previously presented.

The **original elements** of this doctoral thesis refer to the following aspects:

- the use of expired drugs as leveling agents in acid copper and nickel plating baths;
- the use of novel expired drugs as corrosion inhibitors for copper in nitric acid and carbon steel and nickel in sulfuric and hydrochloric acid;
- establish correlations between the molecular characteristics of drugs active substances and their ability to inhibit the cathodic metal deposition and anodic ionization processes.

Part of the experimental findings from the doctoral studies have been disseminated through the publication of 21 scientific papers, of which 6 are indexed ISI (**FIC: 14.21**), 4 ISI Proceedings, and 11 BDI, and through participation at multiple international and national conferences. Of these, in the field of the PhD thesis, 4 published scientific papers are indexed ISI (**FIC: 8.92**), one ISI Proceedings, 4 BDI, and 9 papers were presented at international and national conferences.

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