Electrochemistry for a Cleaner Environment

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INTRODUCTION.

The cathodic cleavage of disulphides is a very well documented, [1-8], efficient and useful method for obtaining pharmaceuticals such as L-cysteine and homocysteine and related products such as N-acetyl-L-cysteine, S-carboximethyl-L-cysteine and acetyl homocysteine. All these products can be synthesized from L-cystine and homocystine which are both obtained from natural sources.

The chemical synthesis of L-cysteine or homocysteine is normally carried out by the reduction of L-cystine (homocystine) to L-cysteine (homocysteine) using classic inorganic reductants such as Zn and Sn. However, there are several drawbacks to all these chemical reductions. First of all, they produce big quantities of hydrogen and metallic ions which pollute the effluents and the disposal of these has to satisfy the ever more stringent laws for industrial pollution. Secondly, the metallic ions can, very easily, contaminate the final product which must also be purified to reach the standard required of pharmaceutical products.

However, the electrochemical synthesis of these compounds has very high material and current efficiency and avoids the use of power metals. By this means, the problems caused by the presence of the metallic ions and by strong hydrogen evolution is eliminated.

From 1988 until now, the group of Applied Electrochemistry of the Physical-Chemistry Department of the University of Alicante has been carrying out research work with the aim of developing and optimising the synthesis of these organic compounds by electrochemical means. The use of Electrochemical Technology leads to a great decrease in pollution together with a bigger capacity for the control of the selectiveness and efficiency of the process. If to all these advantages we add the excellent quality of the final products obtained we can see how competitive and efficient is the use of Electrochemical Technology in the pharmaceutical industry

Several processes of synthesis of L-cysteine and homocysteine and related products have been developed during this period and fig.1 shows a scheme of the process optimised by the group during these years.

These processes have been scaled up from a voltammetric study to industrial or pre-industrial scale in accordance with the following methodological approach:

METHODOLOGICAL APPROACH.

1.- Voltammetric study.

First of all a voltammetric study of the electrochemical process was carried out with regards to the global aspects of electrodic mechanism such as reversibility; types of processes that controls the current; types of electrode materials to be used; the values of the current density to be employed, the type of electrolyte and pH; temperature, etc. By using this approach, important information about the viability of the electrochemical process can be obtained at a low cost and few laboratory experiments. Fig.2 shows a voltammetric curve of the reduction of L-cystine on a lead electrode in acid and basic media. A well defined peak is obtained that appears at less negative potentials than that of hydrogen reduction and this leads one to expect that the synthesis of L-cysteine will have high current efficiency. The possible cathodic materials can now be chosen and also the most convenient conditions in which to carry out the preliminary syntheses.

2.- Laboratory study.

A laboratory electrolysis system (fig. 3a) composed of a divided filter press cell (fig. 3b), two pumps, two thermostatic tanks, a power source and auxiliary material was employed. The filter press cell was designed and built at the laboratory. The electrodic areas change from 20 to 60 cm^2. During this step the parameters studied were the type and nature (two or three dimensions) of the cathode and the anode; the possibility of using either a normal separator or an ion exchange membrane; the current density to be used; the concentration of the initial product, the temperature, pH, the material and current yields, the purity of the product, etc..

For all cases (routes 1 to 5 in fig.1) the anodic process was normally oxygen evolution. Figure 4 shows a scheme of the L-cysteine process. However here, it can be pointed out that for the synthesis of L-cysteine in sulphuric medium the oxidation of L-cystine to cysteic acid was used as anodic reaction and optimised with very good results. Other anodic process can be used for the homocysteine process, as we will see.

3.- Pre-industrial scale study.

Once previous study of this kind was finished, pre-pilot studies are normally undertaken with the aid of a contract with an industry. The studies are carried out in the electrochemical pilot plant of the University of Alicante, (figs. 5) designed and built by our Group of Applied Electrochemistry. The characteristics of this plant are:

A filter press cell with electrodes of 1000-2500 cm^2 unitary area
Rectifier of 30V-1000A computer controlled.
Two 1 m^3 tanks for anolyte and catholyte.
Auxiliary systems (pumps, data acquisition and control, etc.)

In all cases the results obtained in the pre-industrial study were very similar to those obtained in the laboratory.

RESULTS.

The research carried out until now has been as follows:

1st) Route 1 was published in 1989[2]. The results corresponding to the coupling of the oxidation of L-cystine to the synthesis of L-cysteine has also been published [3].

2nd) Route 2 was developed in collaboration with the chemical industry DSM Deretil S.A. A confidential agreement avoids any publication but the process has been patented [4]. This process was developed to industrial scale and 14,000 kg of S-carboxy methyl-L-cysteine were obtained in our pilot plant in a period of approximately 1,000 hours of electrolysis. The process has been transferred to DSM Deretil and is working smoothly at this moment.

3rd) Route 3 was developed by our group to pre-industrial scale. The process is PCT patented [5] and can be transferred or licensed for industrial use.

4th) Routes 4 and 5 were developed in collaboration with Prodesfarma. During the period 1989-1991 the process was optimised to pre-industrial scale. A total amount of 400 kg was obtained in our pilot plant before the synthesis was transferred to Prodesfarma. Until now a total of 400-500 metric tons has been obtained. Several patents have been requested and obtained [6, 7].

Electrochemical Synthesis of DL-homocysteine.

DL Homocysteine is a key intermediate for the synthesis of citiolone, a powerful agent used to treat bronchitis and colds. This compound is obtained through cathodic reduction of DL homocystine which is obtained from the digestion of methionine in sulphuric acid.

The overall process is composed of the following steps:

1st) Methionine is transformed in DL homocystine through digestion with sulphuric at 115 ^{o}C.

2nd) DL homocystine is electrochemically reduced by using a divided filter press cell at constant current (between 100 to 200 mA/cm^2) with a modified carbon felt electrode as cathode. Under adequate conditions this compound can be transformed to Homocysteine thiolactone by cyclation. The oxidation of the SO_2 formed during the digestion has been selected as anodic reaction (fig 6). The SO_2 is absorbed on a basic solution using a scrubber and transformed during the reaction to sulphate. This avoids the formation of chlorine, see fig.1, and the pollution caused by this gas and SO_2 and shows an elegant example of coupling a synthetic process with an electrochemical effluent treatment.

3rd) Citiolone is obtained from thiolactone by acetylation.

This process has been scaled up to pre-industrial dimensions in our pilot plant using a divided filter press cell and a modified carbon felt cathode. The current density used was 300 mA/cm^2 and the electrolyte was a 0.8M DL Homocystine in 4,5M HCl solution at 45 ^{o}C. The total cathodic area was 4x 1000 cm^2 and a total amount of 400 kg of thiolactone was obtained. The energetic cost is 1,1 kWh/kg and the production, at this current density of 300 mA/cm^2, was 265 kg/m^2.day (fig. 7a and 7b). After 200 hours of electrolysis the corrosion of the electrodes and the cathode and anode current feeder was very low. The cell, designed and built in our laboratory, was assembled in a bipolar way and special precautions were taken in order to avoid shunt current losses.

Electrochemical Synthesis of S-carboxymethyl-L-cysteine.

S-carboximethyl-L-cysteine can be obtained in one step by the reduction of L-cystine in basic medium in the presence of monochloroacetate anions that are added during the electrolysis (fig. 8). This procedure avoids the separation, isolation and neutralisation of L-cysteine. A three dimensional carbon felt electrode can be used and so the contamination by metallic cations is avoided and at the same time, the material yield is increased. All this yields a final product exempt of L-cystine and without the need of a posterior purification step.

The experimental conditions for electrolysis were:

Cathode: a carbon felt electrode modified to obtain a high current efficiency.

Catholite: L-cystine in aqueous NaOH. Initial concentration 0.8-1.3 M. pH between 8 and 13.5

Anode: A Dimensionally Stable Anode, DSA.

Anolite: Aqueous Na_2SO_4.

Separator: Neosepta CMX cationic membrane.

Current density: 250-2000 A/m^2.

Temperature: 40-50 ^0C.

The economic parameters were:

Electric cost: 1.0 kWh/kg. Production: 190 kg/m^2.day.

Electrolysis was carried out in a batch mode using a filter-press cell of 9 x 2500 cm^2 total cathodic area (bipolar mode). The number of batches were 132 and the accumulated electrolysis time was 1000 hours. The material and current yield was always very high and very stable during the final period of the electrolysis (fig. 9). The total amount obtained in the pilot plant of the University of Alicante was 14 metric tons (before crystallization) and Table 1 shows a representative analysis of the product that indicates that the purity of the final product meets the requirements of European Pharmacopea.

Contents	***>98,5 (normally 99,5%)***
Specific rotation	***–33,0 to 35,0 (c = 10%, pH = 6.3)***
Residue on ignition	***<0.3%***
Clarity	***Clear***
Chloride content	***<0.15%***
Related substances (Cys2/Cys)	***<=0.5%***
Heavy metals	***<10 ppm***

Table 1

Electrochemical Synthesis of N-acetyl-L-cysteine.

This compound is also used for the treatment of bronchitis and colds. The overall electrochemical process is composed of several steps:

1st) N,N' diacetyl L-cystine is obtained by acetylation of L-cystine with acetic anhydride in basic medium.

2nd) Sodium acetate is removed from solution by electrodialysis using a standard electrodialytic cell.

3st) Electrochemical reduction of N, N'acetyl-L-cystine at constant current using a divided filter press cell with a modified carbon felt electrode yields N acetyl-L-cysteine.

4th) N acetyl-L-cysteine is separated and crystallised from the solution using standard procedures.

The material and current yield is very high while production and energetic cost are very low. The quality of the product is very high and meet with the requirements of the European Pharmacopea:

Contains	***88.2%-100.2%.***
Specific rotation	***+21^{o} to +27$^{o.}$***
Residue on ignition	***<0.5%.***
Loss on drying	***<1%.***
Heavy metals	***<10 ppm***
Arsenic	***<5 ppm***

The principal advantages of the electrochemical synthesis are:

⊗Salts generated during the acetylation are removed.

⊗The intermediate product, N,N' acetyl L-cystine, is not isolated and due to the existence of minimum quantities of hydrogen generated electrochemically an inert atmosphere is not needed to avoid the oxidation of N,N' acetyl L-cystine.

⊗It is an environmental friendly method.

⊗Easily computerised and automatised.

⊗The number of steps in the overall process is minimal

The process has been patented by the University of Alicante

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