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Industrial Synthesis of Cysteine Derivatives

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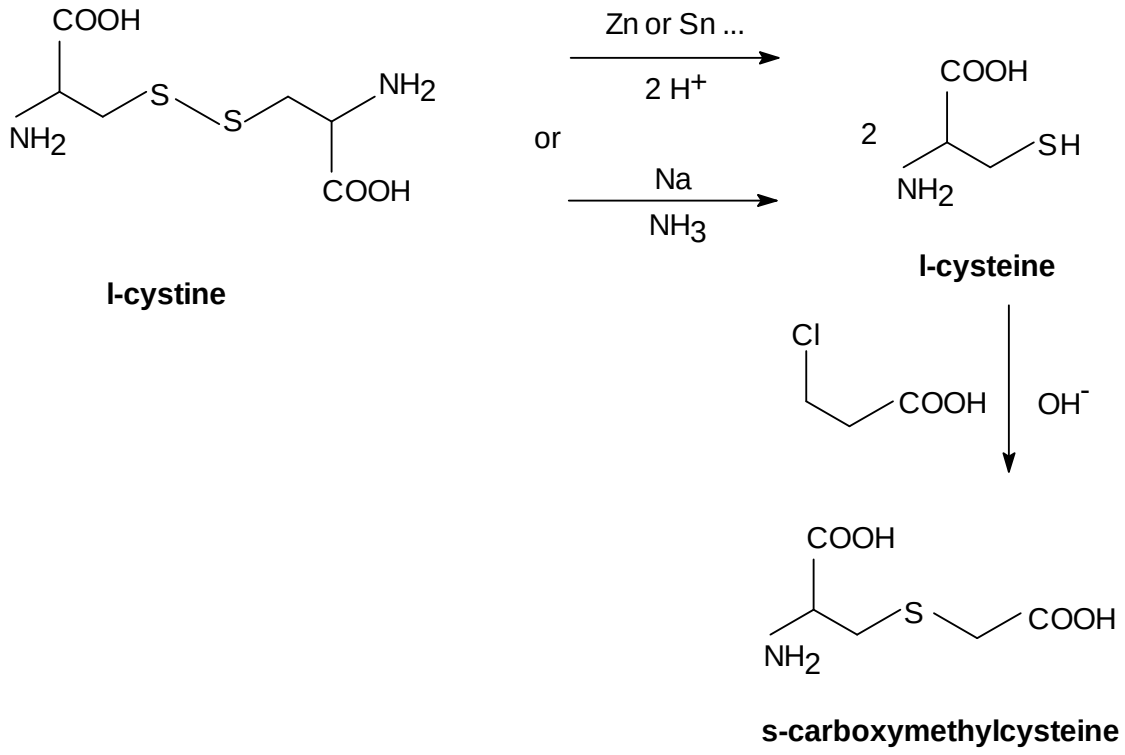
INTRODUCTION.

S-carboxymethyl-l-cysteine is a very important pharmaceutical product with mucolitic activity and is normally used for the treatment of bronchitis and colds.

Chemical synthesis of this product is normally carried out by the reduction of cystine to cysteine using the classics inorganic reductants[1,2] as Zn, Sn and HSO_3^- followed by the reaction of the cysteine with monochloroacetic acid, Figure 1.



l-cystine

l-cysteine

s-carboxymethylcysteine

fig. 1

There are several drawbacks to all these chemical reductions because they produce big quantities of hydrogen and metallic salts and effluents with high salinity. The waste water coming from this synthesis is highly contaminating and its disposal must meet with the

ever more stringent laws for industrial pollution. Moreover, the quality of the cysteine obtained after the reduction process is not very good and so the S-carboxymethyl-l-cysteine must be purified to reach the standards of pharmaceutical products; this increases the complexity and the cost of the process.

Electrochemical synthesis.

The cathodic cleavage of disulphides is a very efficient, useful and very well documented method for obtaining pharmaceuticals such as l-cysteine, homocysteine and their related products[3]. This cathodic reduction proceeds with a very high material and current yields and avoid the use of powder metal, eliminating the problems caused by the presence of the metallic ions in the effluents and by the strong hydrogen evolution. Normally, l-cysteine is obtained as chlorhydrate by reduction of cystine in HCl medium using metallic cathodes of high hydrogen overpotential such as Zn, Sn or Pb. If especial precautions are not taken the final product can easily be contaminated by metallic ions.

Once l-cysteine has been obtained two procedures for obtaining S-carboxymethyl-l-cysteine can be used, Figure 2.

1.- Separation of the chlorhydrate and posterior coupling with monochloroacetate in basic medium.

2.- Neutralisation of the solution containing the chlorhydrate and addition of the monochloroacetic acid.

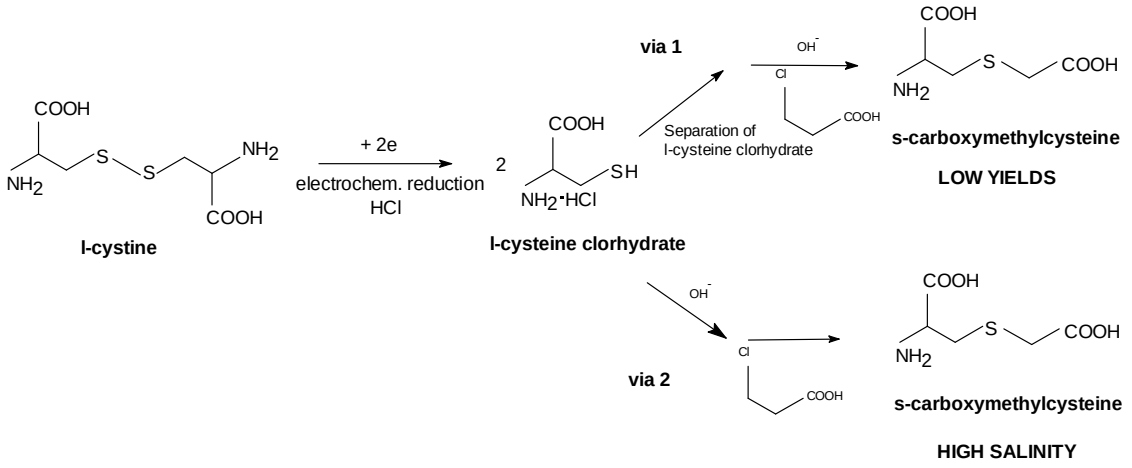
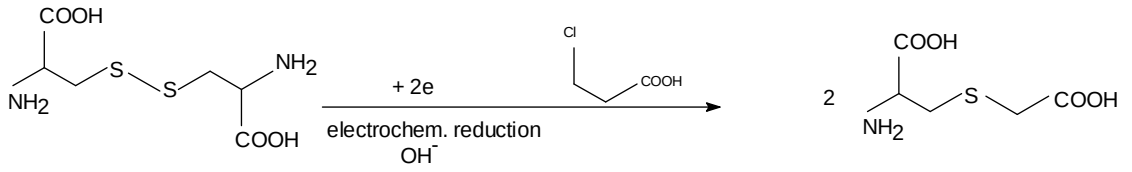


fig.2

The separation and isolation of the chlorhydrate is difficult and the final yield is low whilst neutralisation and addition of monochloroacetic acid produces a solution with high salinity making difficult the isolation of the final product. Moreover, using these metallic cathodes the reduction of the cystine is not total and a small quantity of the initial product is always found decreasing the quality of the product i.e. a posterior step of purification must be introduced.

One step electrochemical synthesis.

The reduction of l-cystine to l-cysteine can be carried out in a basic medium in the presence of monochloroacetate anions that are added during the electrolysis. This procedure avoids separation, isolation and neutralisation steps and if the reduction is carried out using a modified carbon felt cathode the contamination of the product by metallic cations is avoided and at the same time the material yield is increased. These benefits permits the obtention of a final product exempt of l-cystine and without the need of a posterior purification step.



l-cystine **s-carboxymethylcysteine**

fig.3

Starting from a voltammetric study the process has been scale up to an industrial process according with the following steps:

Laboratory and pre-pilot study.

After a voltammetric study of the electrochemical process in which the global aspects of the electrodic mechanism has been dilucidated (reversibility, nature of the process that controls the current, type of electrode materials to be used, values of the current density to be employed etc.) the electrochemical synthesis of S-carboxymethyl-l-cysteine at a laboratory scale has been carried out.

Initially, a laboratory electrolysis using a cylindrical glass cell with electrodes of $3cm^2$ of area separated with a cationic membrane has been used to identify the final product and to determine several parameters, that we will need during the pre-pilot study, such as type

and nature of the electrodes anode and cathode, influence of the type of membrane, possibility of using a normal separator, material and current yield of the synthesis, purity of the product...

Once this study was finished, we started a prepilot synthesis using a dived filter press cell with electrodes of 200 cm^2, two electrodes, designed and built at the University of Alicante. Figure 4 shows a general description of the synthesis.

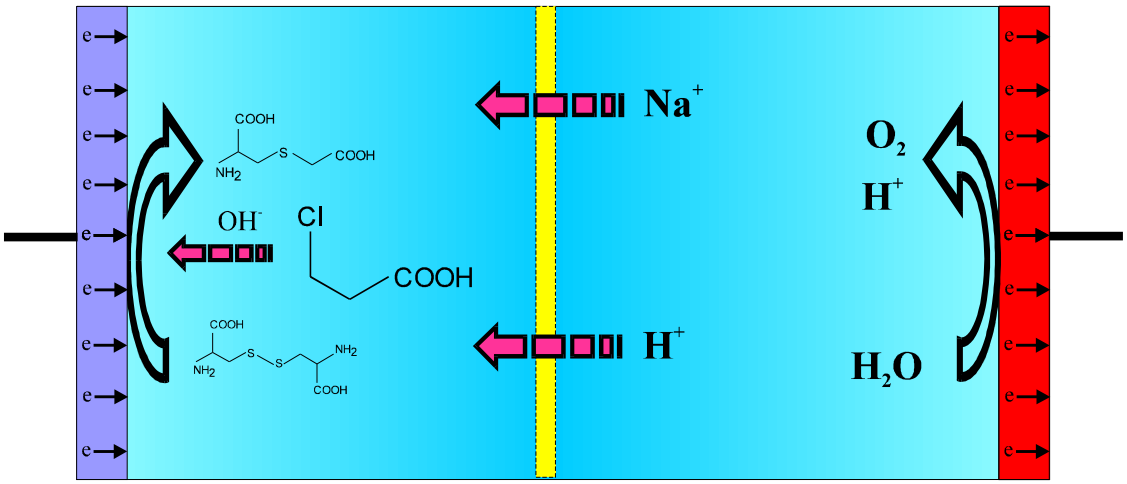


fig.4

This cell was used to carry out a preliminary study of the process in which the material yield relative to the initial product, the energetic cost (kWh/kg) and the production (kg/m^2.day) for a given current, were optimised. The variables studied were:

Cathode and anode materials.
Type of separator
Influence of the initial concentration of l-cystine and pH
Current density
Temperature

Electrolysis was discontinued when the concentration of the remaining l-cystine was lower than 0.5%.

The study permitted us to know the best conditions for electrolysis and the adequate program for the addition of monochloroacetic acid and the best value of pH for the coupling reaction.

The experimental conditions for electrolysis were:

Cathode: a carbon felt electrode modified to obtain a high current efficiency.
Anode: A Dimensionally Stable Anode.
Catholite: l-cystine in aqueous NaOH. Initial concentration 0.8-1.3M. pH between 8 and 13.5.
Anolite: aqueous Na_2SO_4.
Separator: Neosepta CMX, cationic membrane.
Current density:250-2000 A/m^2.
Temperature: 40-50 ^oC.

l-cystine concentration in the final product was always lower than 0.5%. Electrolysis was finished when the electric charge passed was 115-125% of the theoretical charge of 2F/mol. For this percentage of charge the cystine content in the S-carboxymethyl l-cysteine was lower than 0.5%. The rate of addition of monochloroacetic acid corresponds to the rate of formation of l-cysteine.

The economic parameters of the synthesis were:

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

Industrial pilot Synthesis .

Once the pre-pilot study had demonstrated the viability of the process, a scale up of the electrolysis plant to industrial dimensions was carried out at the pilot plant of the University of Alicante with the help and collaboration of DSM Deretil . During this study the best conditions for long time electrolysis were determined together with the procedure for separation and crystallisation of the final product.

Electrolysis was carried out in a batch mode using a filter-press cell of 9x2500 cm^2 cathodic area (bipolar mode) The number of batch was 132 and the accumulated electrolysis time was 10 months. The material yield was always very high and during the final period of the electrolysis very stable, see figure 5. Anode, cathode and membrane behaviour was very good. Minor modifications to the electrolysis and

separation and crystallisation procedures were carried out during these 10 months in order to improve the material yield of the process and the purity of the product. The total amount obtained has been 14000 kg (before crystallisation) and the purity of the S-carboxymethyl-l-cysteine was >99.5%. Table I shows a representative analysis product that indicates that the purity of the final product meets with the requirements of European Pharmacopea.

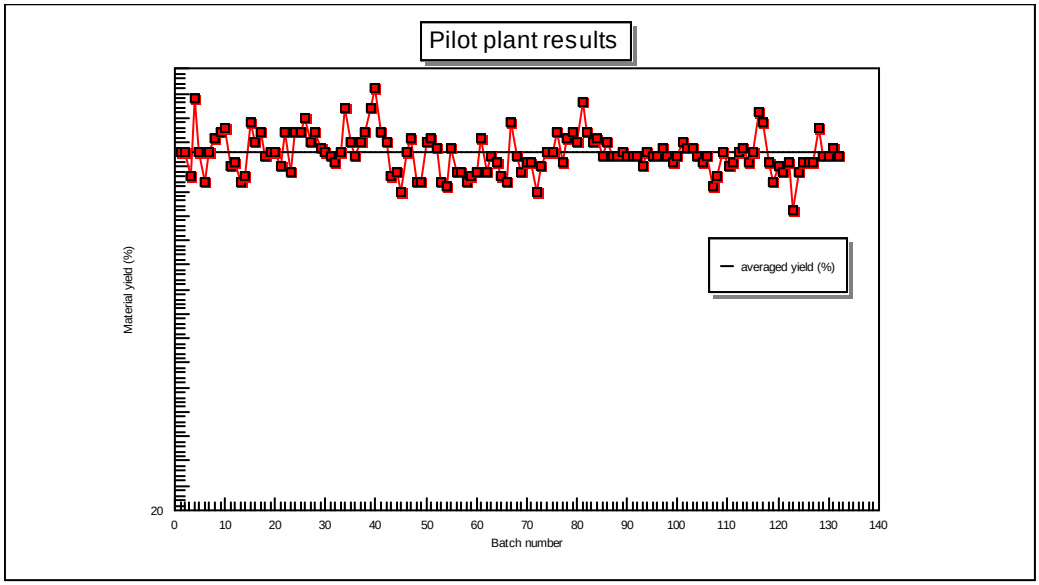


fig.5

From April 1996 the process has been implanted in DSM Deretil

Contents	>98,5%
Specific rotation	-33,0 a -35,0 (c=10%, pH=6,3)
Clarity	clear
Residue on ignition	<0,3%
Chloride contents	<0,15%
Related substances (Cys2/Cys)	<= 0,5%
Heavy metals	<10 ppm

Table I

Conclusions.

The use of the electrochemical technology has permitted the developing of a new one step procedure for obtaining a very interesting pharmaceutical product as is S-CARBOXYMETHYL-L-CYSTEINE avoiding the inconvenient of using metal reductants and improving the purity of the final product.

We have demonstrate that is possible, starting from a voltammetric study, to scale up an electrochemical process to industrial level and to carry on the synthesis of 14000 kg of a pharmaceutical product in an University Laboratory with the help and collaboration of an enterprise.

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