Electrochemical Microinstallation for Cytostatic Wastes Epuration

VALENTIN ORDODI[1]*, GABRIELA-ALINA DUMITREL[2], ALEXANDRA GRUIA[3], MIHAI IACOB[2], GHEORGHIŢA JINESCU[4], DELIA PERJU[2]

[1] University of Medicine and Pharmacy "Victor Babes" Timisoara, Department of Biology, 2A E. Murgu Square, 300041, Timisoara, Romania

[2] "Politehnica" University of Timisoara, 2 Victoriei Square, RO-300006, Timisoara, Romania

[3] Regional Center for Transplant Immunology, Emergency Clinical County Hospital Timisoara, 10 Iosif Bulbuca Bvd., 300736, Timisoara, Romania

[4] "Politehnica" University of Bucharest, Faculty of Applied Chemistry and Material Science, 1-7 Polizu Str, 011061 , Bucharest, Romania

The appearance of cytostatic-cytotoxic drugs in the environment constitutes a threat to ecosystems and human health. The pollution source with such chemicals is represented by waste water from the health institutions which treat patients with oncological diseases. The paper presents a fully automatic experimental installation of small dimensions to eliminate cytostatics from waste water. Testing the installation was done by assessing the performance of depuration of synthetic and real samples with cytotoxic effect – methotrexate. The functioning of the experimental micro-installation, by its original concept, favors unfolding reactions of interest (chemical and electrochemical oxidation) with a minimal consumption of power also providing a minimal duration of electrolysis process.

Keywords: electrochemical reactor, depuration, waste water, cytostatic waste

Spectacular progress of medical science in the past decades led to excellent therapeutic results in various diseases considered incurable until not long ago, but with the price of introducing chemicals in therapy with extremely harmful effects to the environment. Even if these chemicals reach the environment in small quantities and their pollution effect is not immediate, they accumulate over time. This category includes drugs with cytostatic–cytotoxic effect, which are used in the treatment of oncological diseases. Unfortunately, these chemicals are not very selective, they work largely on cancer cells but also affect normal cells especially when administered in large doses. This kind of treatment is recommended in case of oncological diseases that benefit from high dose chemotherapy such as bone marrow transplantation. Non-selective action of cytostatic agents influences their major pollutant potential. Most chemotherapy drugs have carcinogenic, mutagenic and teratogenic effect. Because of these effects these substances affect population health and ecological systems directly and indirectly. They end up in the environment as waste water from health institutions which treats patients with oncological diseases [1].

To eliminate the toxicity of the waste water National Institute of Health SUA recommends incineration of all wastes that contain cytostatics in order to prevent environment contamination, and people exposure respectively. The incineration is however quite difficult to achieve since there are in most cases large quantities of liquid waste (urine especially); incinerators are expensive, power intensive and polluting, releasing into the atmosphere large amounts of carbon dioxide. Analyzing the cost-benefit ratio, International Agency for Research on Cancer (IARC) (1996) recommends chemical treatment with strong acids or bases, and hypochlorite for cytostatic agents' inactivation. However manipulation of concentrated solutions of strong acids or bases is not recommended in hospitals. Sodium hypochlorite is easy to apply solution for chemical inactivation of cytostatics, but it is necessary a continuous quality control of sodium hypochlorite solution that is used [2].

The aim of this study is to design and develop a fully automatic experimental installation of small dimensions in which cytostatics are detoxified utilizing a combined method based both on electrochemical and chemical oxidation in the presence of strong oxidants as free chlorine [3, 4].

Based on an original design, the experimental installation favors the reactions of interest (electrochemical and chemical oxidation) with very low electricity consumption and also provides a minnimal duration of the whole electrolysis process.

Experimental part

Experimental microinstallation and operating mode

Experimental microinstallation is composed of three distinct parts: sample preparation system, electrochemical microreactor and automatic system. In figure 1 is presented the ensemble of experimental microinstallation. Figure 2 shows the scheme of the experimental installation in detail.

Microinstallation contains a preparation system for depuration of the sample that includes a vessel (fig. 2(5)) in which takes place the mixing of the 25% brine solution in order to achieve a salinity of 1 to 10 g NaCl/100 mL. The salinity is established by the operator (following preliminary experimental determinations) depending on the cytostatic which has to be cleared in order to achieve optimal conditions for electrolysis.

The most important part of the depuration system is the electrochemical reactor (fig. 2(11)). This is an electrochemical reactor of small dimensions with asymmetrical current densities which favors electrochemical oxidation reactions of cytostatics that are going to be depurated.

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* *email: valibioch@yahoo.com*

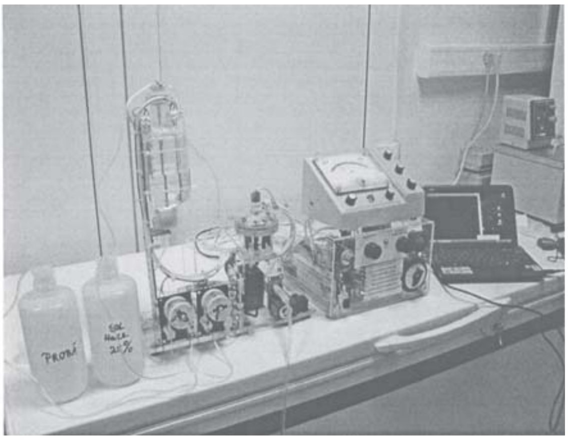

Fig. 1. Experimental microinstallation for evacuation of waste water's cytostatics that comes from medical oncology activity

The operating principle of the microreactor suits the purpose: favors anodic oxidation reactions and generates a large quantity of free chlorine (sodium hypochlorite, hypochlorite acid, physically dissolved chlorine) with a small consumption of electricity in a short period of time. The characteristics of the electrochemical microreactor with asymmetrical current densities are: 100 mL fill volume; a stainless cathode with a 1 mm diameter and 115 mm total length, coiled around a shaft mixer (5 spires with an 5 mm interior diameter) – with a surface (Sc) of 3.61 cm^2 and cathode current density of 2,770 A/m^2; 8 anodes of graphite with 6 mm diameter and 30 mm working length with a total surface (Sa) of 45.21 cm^2 and cathode current density of 221 A/m^2. The shaker of the device is "with pallets" type, operated by an electric motor and rotates with 30 rot/min. The Sa/Sc ratio is 12.5, the relative anode – cathode distance is 25 mm and the maximum working current is 2 A.

Basic diagram of the experimental device is presented in figure 2. The hydraulic and pneumatic components, material flows, and the placement of related sensors are highlighted. The electronic control system is activated by process computer. This emits the necessary commands using specialized software written especially for this device and includes management algorithms of automatization which assures the optimal functioning of depuration microinstallation [5].

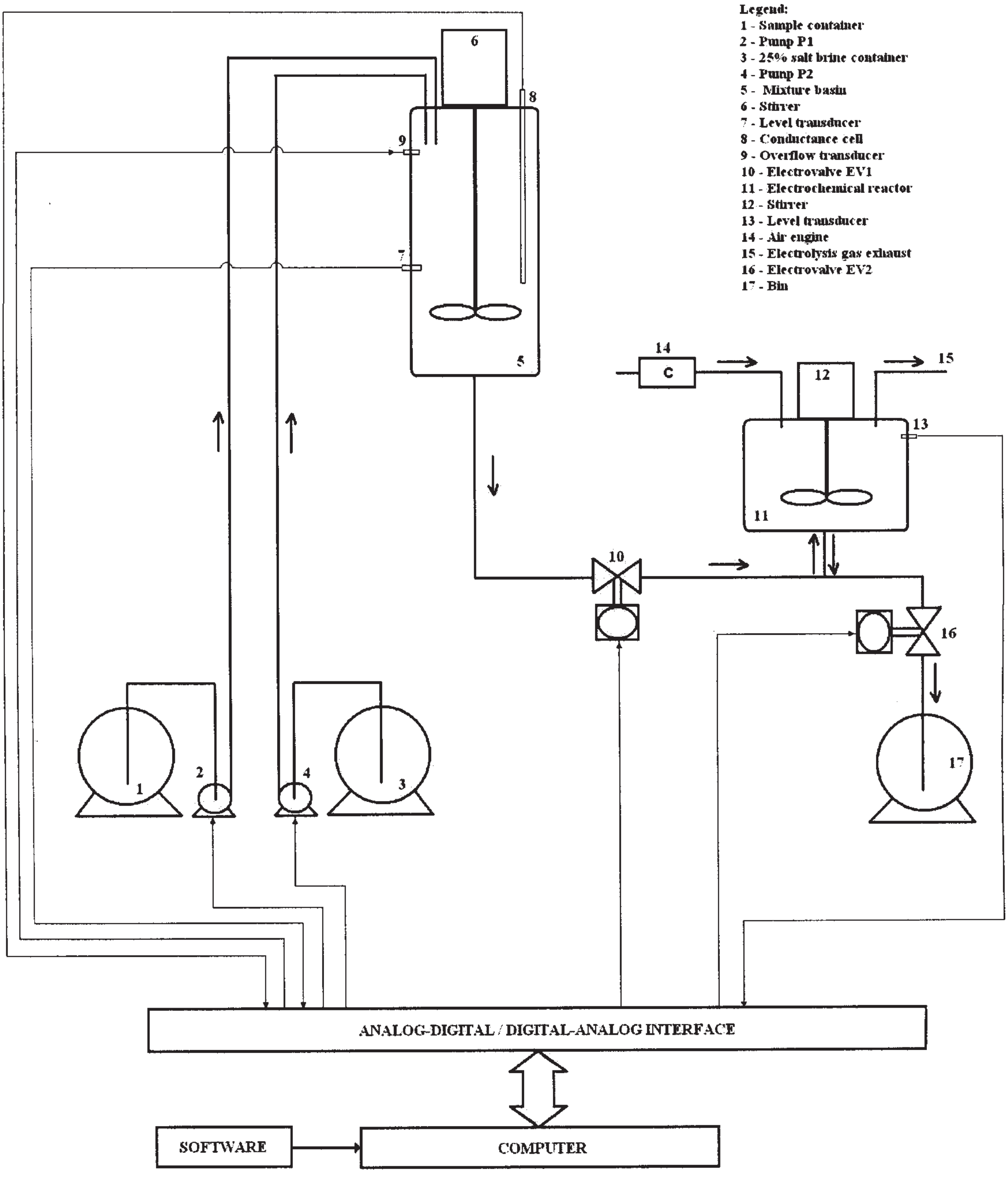

Fig. 2. The simplified chart of the depuration system activity

The sample that contains cytostatics which have to be depurated is suctioned with a P1 peristaltic pump (fig. 2(2)) from the reservoir with waste water. This goes to the mixing vessel (fig. 2(5)) that fills up to a 300 mL volume, level detected with a conductance sensor (fig. 2(7)) which stops P1 pump when the vessel is filled up. The mixing vessel is provided with a shaker device (fig. 2(6) which homogenizes continuously the sample. When the sample is all taken up the P2 pump starts (fig. 2(4)), which introduces 25% brine solution from reservoir 2. (fig. 2(3)). A conductance cell (fig. 2(8)), that exists in the mixing vessel, measures permanently the conductance of the sample, and thus indirectly its salinity. The conductance of the sample increases as the brine volume increases; this could be detected by the electronic device, which through the computer stops P2 pump when is reached the salinity set up previously. In this moment the content of the mixing vessel (which includes the cytostatic in saline solution) is send to the electrochemical micro-reactor. There is another sensor (fig. 2(9)), which is placed at the upper edge of the mixing vessel that sounds an alarm in case of abnormal functioning of a pump, a level sensor of the sample, or conductance cell, and stops the whole installation when is reached a maximum level of the volume in the mixing vessel.

Filling of the electrochemical micro-reactor (fig 2(11)) is achieved by free flow. On the supply route there is an EV1 electrovalve (fig. 2(10)), which is open until is reached a maximum level in the electrochemical reactor, detected by a conductance sensor placed in the reactor (fig. 2(13)). Electrolysis starts under a constant current when the microreactor is full. During electrolysis the reaction mixture is homogenized with a shaker placed into the reactor (fig. 2(12)). Electrolysis current is adjustable in the range of 0–2 A and is constantly maintained by an automatic electronic device, in order to avoid its increase as the electrolyte warms up. The electrochemical microreactor is emptied through the EV2 electrovalve (fig. 2(16)) in a collecting vessel (fig. 2(17)) after the electrolysis ends. The process automatically restarts after the electrochemical microreactor is emptied and a new volume of probe solution reaches the electrolyzer in order to be treated.

Both mixing vessel and electrochemical microreactor have connection hoses to collect samples during the electrolysis process for physical and chemical analysis.

The electrochemical microreactor has also a system for elimination of gases resulted from electrolysis process, that are evacuated outside the workspace (fig. 2, (14, 15)) [6].

Assessment of the experimental microinstallation

Determination of free chlorine production

For all determinations a 5 g/100 mL sodium chlorine solution was used. The free chlorine production was assessed and expressed as mg of free chlorine per 1000 mL electrolyte.

Dosage of free chlorine (sodium hypochlorite, hypochlorite acid, and physically dissolved chlorine) was made by titration with methyl orange in acidic media.

The production of free chlorine was monitored for 90 minutes at an electrolysis current of 1 A [7].

Depuration of waste waters that contain Methotrexate

Methotrexate (MTX) is a drug with cytotoxic effect that acts as folic acid antimetabolite. Methotrexate is eliminated in its active form mostly by urine (80%) within 24 h that reaches the environment with the urine of the treated patients. Pollution becomes significant in case of patients who receive increased doses of MTX: 5-12 g/m^2 body surface. A lot of nine patients were treated with high doses of methotrexate; they received 8.8+/-5.2 g methotrexate within 4–24 h of endovenous perfusion, depending on the therapeutic approach. All patients were parenterally hydrated. The medium concentration of the urinary methotrexate was of 175+/-46 mg/dL for a 2.500-4.800 mL/24 h urinary volume. It was also prepared an artificial sample of waste water that contains 200 mg/dL methotrexate. The ten samples were subjected to depuration using the above-mentioned microinstallation. Depuration duration was 90 min, since the concentration of free chlorine is stable at that time point [8, 9].

An informed consent was completed for each patient that provided a sample of urine, and the bioethics committee of the University of Medicine and Pharmacy “Victor Babes” Timisoara, approved the experimental procedures.

The methotrexate concentrations were detected using high performance liquid chromatography (HPLC) on an Agilent 1100 series. HPLC analytical conditions were the following: mobile phase: 80% water at pH=5 (acidified with phosphate buffer) and 20% acetonitrile, flow rate of 1 ml/min, the injected volume was 20 microliters on a Zorbax SB-C18 column, at 25° C, the detector was set at 373 nm, and the acquisition time for each sample was 10 min.

Results and discussions

Experimental microinstallation generates sufficient quantities of free chlorine and allows efficient MTX depuration both in the artificial sample and urine samples from MTX-treated patients (table 1).

The amount of free chlorine generated during 90 min of electrolysis is presented in figure 3.

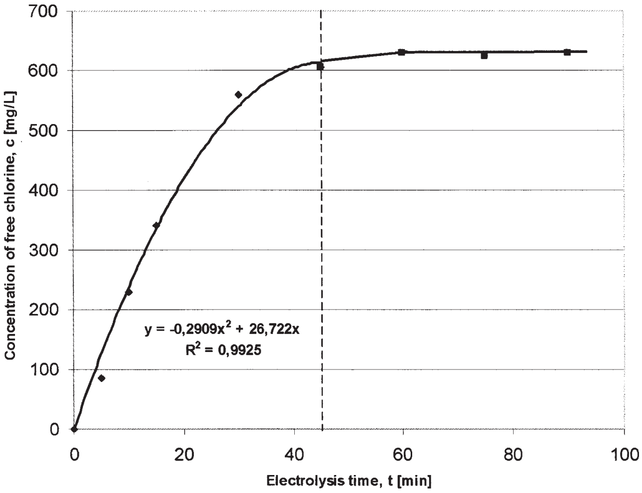

Fig. 3. Free chlorine production during 90 min of electrolysis at a current of 1 A

The generation of free chlorine becomes constant after 90 min . In the first 45 min the increase in the amount of free chlorine follows an order 2 polynomial equation

$$C = -0.2909t^2 + 26.722t \qquad (1)$$

which indicates that the duration of the electrolysis process is recommended to be longer than 45 min.

The evolution of the MTX concentration during depuration of artificial waste water and the urine samples from the nine patients is presented in table 1.

Figure 4 shows the variation of MTX concentration from artificial sample during electrochemical depuration process obtained by regression curve [10]. From the chart it can be

Table 1
THE MTX CONCENTRATION EVOLUTION DURING DEPURATION OF ARTIFICIAL WASTE WATER AND URINE SAMPLES

Time [minutes]	0	5	10	15	30	45	60	75	90
Artificial sample MTX [mg/dL]	200	162	127	90	51	23	8	6	3
Sample 1 MTX [mg/dL]	198	165	130	88	50	25	8	4	2
Sample 2 MTX [mg/dL]	156	120	89	50	31	14	6	9	5
Sample 3 MTX [mg/dL]	221	178	145	108	68	26	12	8	3
Sample 4 MTX [mg/dL]	212	168	121	91	48	21	11	4	2
Sample 5 MTX [mg/dL]	138	100	72	28	17	9	6	4	2
Sample 6 MTX [mg/dL]	186	160	123	79	38	22	7	3	2
Sample 7 MTX [mg/dL]	129	95	63	24	15	7	5	4	2
Sample 8 MTX [mg/dL]	154	121	88	53	27	12	6	4	2
Sample 9 MTX [mg/dL]	135	102	70	27	14	7	5	5	3

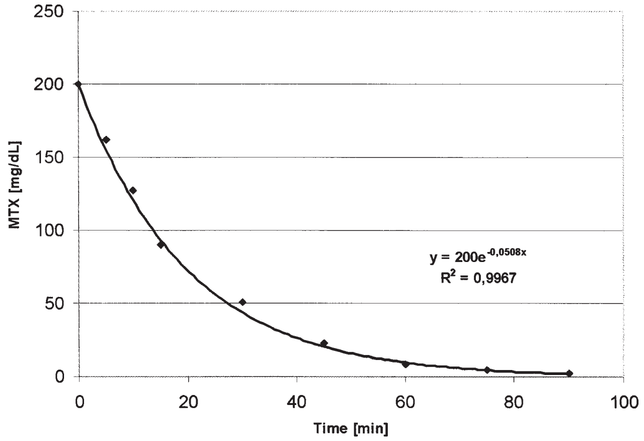

Fig.4. Variation of MTX concentration from artificial waste water during depuration process

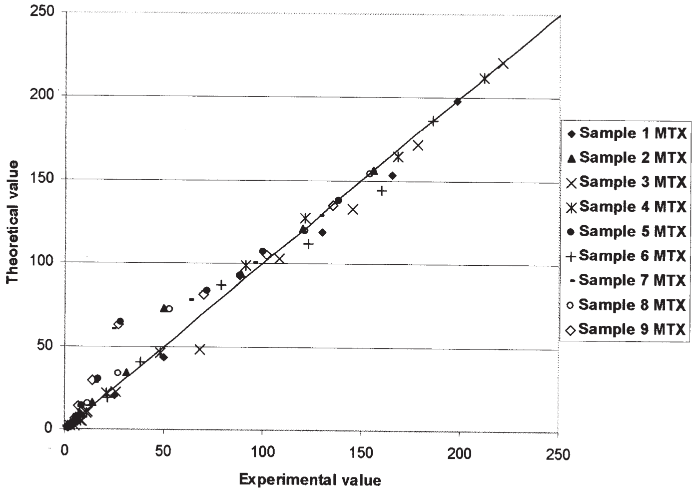

Fig. 5. Experimental data obtained after depuration process of samples of the nine patients and that obtained as a result of applying equation of variation of MTX concentration in the arficial sample

noticed that the decrease of MTX concentration follows an exponential equation:

$$C_{MTX} = 200 \cdot e^{-0.0508 \cdot t} \qquad (2)$$

The value of correlation coefficient (0.9967) indicates that this equation approximates very well the evolution of MTX concentration during depuration process.

The analysis of the experimental data obtained after depuration process of the samples from the nine patients indicates a variation in the MTX concentration. This variation is similar to the one obtained from the depuration process of the artificial sample. Therefore, by comparison the equation of variation of MTX concentration in artificial sample with that of the evolution of MTX concentrations in urine samples it was noticed a good degree of similarity, suggesting that the method can be successfully applied to all samples from the patients treated with MTX. [11].

Consistency of experimental data obtained after depuration process of samples of the nine patients and that obtained as result of applying equation of variation of MTX concentration in artificial sample is depicted in figure 5.

Depuration average efficiency (η_{MTX}) of methotrexate from urine samples after 90 min is:

$$\eta_{MTX} = 100 - \frac{\overline{c_{MTX\,efluent}}}{\overline{c_{MTX\,afluent}}} \cdot 100 = 98.2\% \qquad (3)$$

Conclusions

Experimental microinstallation allows depurating cytostatics (methotrexate) with good efficiency, in a short period of time and with a reduced consumption of power.

An electrochemical microreactor with asymmetrical current densities is superior to the electrochemical reactors with electrodes with equal surfaces because it favors the reaction of interest: in this case the anode electro-oxidation of MTX.

This microinstallation of depuration has several advantages: reduced weight, good functional performances, and increased depuration efficiency. These advantages recommend utilization of such depuration installations based on the described principles and concepts, for use in the treatment of waste waters produced by medical institutions with oncologic profile.

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