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Flow amperometric determination of pharmaceuticals with on-line electrode surface renewal

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Abstract

In this article, a flow system developed for the amperometric determination of a great variety of pharmaceuticals that are known to lead the rapid poisoning of the working electrode surface is described. The referred system was made up of two parallel flow channels that shared the voltammetric detector of tubular configuration, whose movement in the manifold followed the concept of multi-site location of detector. In this way, after each measurement, the conditioning of the working electrode was possible through the passage by its surface of a regeneration solution without implying the alteration of the carrier that flowed in the analytical channel of the manifold. The methodology proposed was evaluated through the determination of two drugs belonging to two distinct therapeutic groups: an antihypertensive (diltiazem) and a non-steroid anti-inflammatory (nimesulide). The results obtained after evaluation of various pharmaceutical formulations on the Portuguese market were in the case of diltiazem compared with those supplied by the reference US Pharmacopoeia XXIV method, with no statistically significant differences having been observed for a confidence interval of 95%. In the case of nimesulide, since no official reference method exists, a series of recovery experiments were proceeded with and a mean value of 101.1% with a R.S.D. of 0.7% was obtained.

Keywords: Diltiazem; Nimesulide; Adsorption; FIA; Tubular electrodes

1. Introduction

In the analysis of drugs, electroanalytical chemistry has been shown to be an exceptional method and quite often superior to classical wet methods and spectrophotometric methods [1]. However, electrochemical determinations are on many occasions compromised by the fact that numerous drugs led to a progressive passivation of the electrode surface, originating the attainment of irreproducible results or even the complete inhibition of the electronic transfer processes [2,3].

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The insertion of electrochemical sensors in flow systems contributed to the minimisation of poisoning of the working electrode surface, given that it reduces the period of contact of the sample with the electrode [1]. However, and unfortunately, it is not sufficient to guarantee a stable response in the analysis of several pharmaceutical drugs [4].

Therefore, the development of processes that contribute to a stable response provided by voltammetric detectors is essential. Several methodologies have been studied in this context: mechanical polishing [5], heat treatment [6], laser activation [7], dispersion of metal oxides [8] and electrochemical pre-treatments [2,9–12] among others. Despite being effective, some of these renewal processes are time consuming while others require sophisticated equipment. Regarding the more widespread procedures (mechanical polishing and electrochemical pre-treatments) they frequently require the removal of the working electrode from the detector [5] and/or the substitution of the analytical solution (dismounting of the electrochemical cell) since many of the electrochemical pre-treatments are carried out in solutions whose chemical composition is distinct from the support electrolyte [12].

In this article, we describe a general process of regeneration of the glassy carbon electrode surface, by washing it with a conditioner solution, without the need to remove the electrodes from the measurement cell. For such, an FIA system was developed based on the concept of multi-site location of the detector [13]. The system referred to allowed the movement of the detector cell between two distinct flow channels: in the first, the determination of the sample occurred and in the second, the regenerator solution of the electrode flowed. In this way, each measurement alternated with a conditioning of the electrode surface. Given that the quality of the results obtained with the multi-site approach can be limited by the dead volume and configuration [13] of the detector, an electrochemical cell of tubular configuration was constructed, with similar internal diameter to the tubing of the FIA system and with reduced dimensions.

The evaluation of the analytical usefulness of the referred approach was processed through the quantification of two drugs: diltiazem, (2S-*cis*)-3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one, a calcium channel blocker commonly used in the treatment of angina pectoris with probable efficacy as an antiarrhythmic and antihypertensive agent [14] and nimesulide, *N*-(4-nitro-2-phenoxyphenyl)methanesulfonamide, a non-steroidal anti-inflammatory agent administered for a series of painful and inflammatory states [15]. The option of illustrating the good performance of the system developed through the quantification of these two drugs is based on the fact that both lead to a rapid deactivation of the glassy carbon surface. Also, and more important, the methodologies described so far, which could possibly be applied in the quantification of these drugs in pharmaceuticals, are scarce.

A survey of the literature revealed that diltiazem has been quantified in dosage forms mainly by spectrophotometry [16,17] and HPLC with UV detection [18–20]. Only two voltammetric studies of diltiazem were developed [21,22]. The referred methodologies permit the analysis of samples of diltiazem at concentrations lower than 1×10^{-5} M [21], so that although they can be applied in the determination of this active compounds in pharmaceutical formulations after previous dilution they have been shown to be particularly adapted to the determination of diltiazem in biological fluids.

As for nimesulide, it is not yet official in any pharmacopoeia and has been determined by spectrophotometry [23,24], voltammetry [25,26] and HPLC with UV [27] or electrochemical [28] detection. The referred electrochemical methodologies compare favourably with the spectrophotometric methods developed to date, namely in respect of selectivity [25], presenting as their main limitations the low analytical rates attained (never > 12 samples h^{-1}) and the need to proceed with extensive dilutions of samples of pharmaceutical formulations [25,26,28].

2. Experimental

2.1. Reagents and solutions

All chemicals were of analytical reagent grade and Millipore Milli-Q water (conductivity <0.1 μS cm^{-1}) was used in the preparation of all solutions.

In studies involving the determination of diltiazem, the support electrolyte (pH 7.4), which worked simultaneously as carrier, was made up by the $H_2PO_4^-/HPO_4^{2-}$ pair and prepared mixing 800 ml of a K_2HPO_4 solution (0.5 M) with 200 ml of a KH_2PO_4 solution (0.5 M). As the electrode conditioning solution, bi-deionised water was used.

In the nimesulide determination an ethanol/Britton–Robinson buffer mixture (30:70, v/v) (pH* 6.1) was used, simultaneously as support electrolyte and carrier. As conditioning solution an ethanol/Britton–Robinson buffer mixture with an alcohol content of 70% (pH* 6.1) was chosen.

The stock solutions of diltiazem (1.0×10^{-3} M) and nimesulide (2.0×10^{-3} M) were prepared by weighing and dissolving the pure substance in phosphate buffer and ethanol, respectively. Standard solutions used for the calibration curves, whose concentrations were falling between 1.0×10^{-5} and 3.0×10^{-4} M, were prepared from the stock solutions by dilution in the respective carrier solutions.

2.2. Apparatus

In the FIA system developed the solutions were propelled by a Gilson Miniplus 3 peristaltic pump, while the intercalation of the sample plugs in the carrying solution was conducted through an injector–commutator of circular configuration and with identical functioning to that previously described by Krug [29]. The injector–commutator besides functioning as an injector device for the sample plugs, allowed the movement of the tubular voltammetric detector between the two flow channels of the manifold. All tubes and connections were made using 0.8-mm i.d. Omnifit Teflon tubing.

The electrochemical measurements were performed using an AUTOLAB, model PGSTAT10 connected to a microcomputer and printer.

The diltiazem determinations by HPLC, according to the procedure described in the US Pharmacopoeia XXIV [20], were carried out in a Merck Hitachi chromatographic system comprising a pump (7100 model), a Rehodyne 7725i injector (loop of 10 μl) and a Lichrocart RP 18 column (250×4 mm) packed with Lichrosorb 5 μm beads. A Diode Array (model 7000) system was used as detector while the data was processed by the D-7000 software of the same brand.

2.3. Relocatable tubular voltammetric cell

The tubular voltammetric detection cell constructed (Fig. 1), dedicated to the multi-site detection, was made up of a Perspex main body (Fig. 1a) in which a working (Fig. 1, E_w) and an auxiliary electrode (Fig. 1, E_{aux}) were placed, both of glassy carbon and with tubular configuration. These electrodes were built from a carbon rod of 7.0-mm diameter (Goodfellow, VC007940). The working electrode presented a length of 2.0 mm, while the auxiliary electrode was of 1.0-mm length. Both presented an internal diameter of about 1.0 mm. As a reference electrode (Fig. 1, E_{ref}) an Metrohm AgCl/Ag (KCl, 3.0 M) electrode, model 6.0727.000 was used. The electrical contact with the working and auxiliary electrodes was established through two metallic contacts threaded into the Perspex support (Fig. 1b).

The total inner volume of the relocatable detector was determined as being 130 μl according to the procedure for the determination of the injection volume in classic single channel FIA systems [30].

At the beginning of each working day, the glassy carbon electrode was polished through a frictioning of its surface with a thread of wet cotton embedded in alumina powder (Buehler 40-6603-030-016). Residual polishing material was removed from the surface by sonication in a water bath for 1 min.

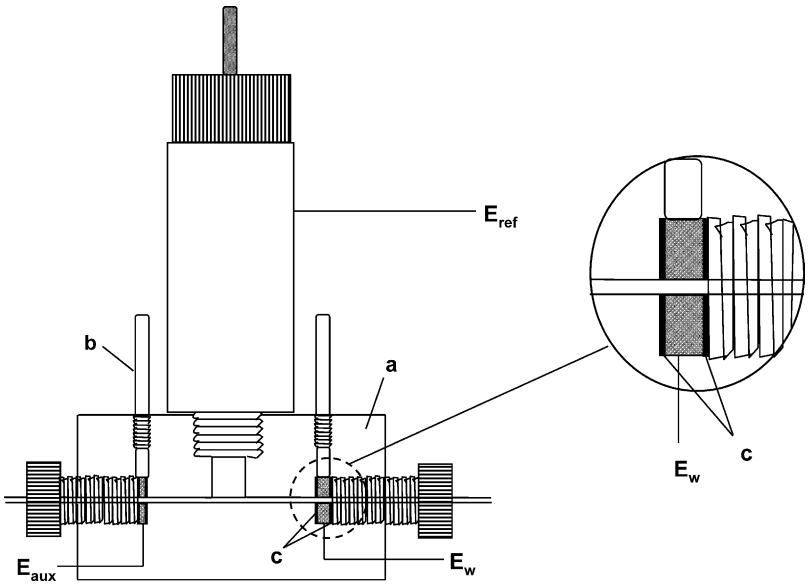

Fig. 1. Schematic representation of the electrochemical cell: E_w, working electrode; E_{aux}, auxiliary electrode; E_{ref}, reference electrode; (a) cell body in Perspex; (b) electrical contact; (c) O-rings.

2.4. Reference procedure

For accuracy assessment of the results obtained by the developed procedure, diltiazem tablets were analysed according to the US Pharmacopoeia XXIV method [20].

Given that there is no reference method for the determination of nimesulide in dosage forms, the quality of the results was evaluated through a series of recovery experiments in the solutions of the pharmaceutical preparations.

For each of the pharmaceutical formulations analysed (tablets), the average weight of each tablet was determined, according to the USP norms [20]. Twenty tablets were then reduced to fine powder and adequate portions of the ground tablets were dissolved in an appropriated solution. The pharmaceutical formulations containing diltiazem were dissolved in methanol for analysis by the USP method and in phosphate buffer for analysis by the proposed methodology. In the case of pharmaceutical formulations containing nimesulide, they were dissolved in an ethanol/Britton–Robinson buffer mixture (30:70, v/v) (pH* 6.1).

3. Results and discussion

3.1. FIA system with multi-site location of detector

A FIA system was established, with two independent channels (Fig. 2A) based on the concept of multi-site location of the detector [13] that made the movement of the electrochemical cell between the two flow channels viable. In this way, each measurement, carried out in one of the channels could alternate with the regeneration of the glassy carbon surface in the other channel through the passage of an adequate conditioning solution, without implying the alteration of the solution that flowed in the channel where the amperometric measurement was carried out. Since the movement of the detector between the two flow channels can be carried out before the complete passage of the sample plug by the surface of the electrode, for example after the attainment of the maximum analytical signal, it is possible to reach a greater sampling rate and reduce the extent of contact of the working electrode with the plug tail. Consequently, the movement of the detector constitutes an advantageous alternative to the redirection of

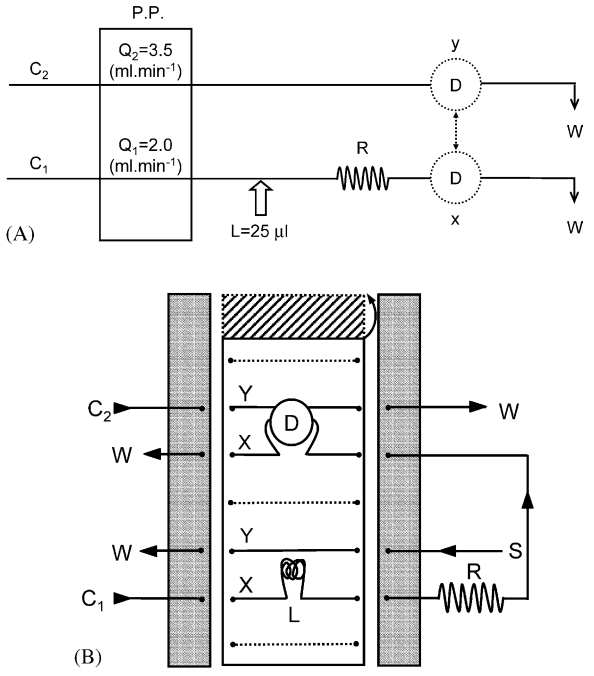

Fig. 2. (A) Flow diagram of the FIA system with multi-site location of the detector (A) and schematic representation of the mode of functioning of the injector–commutator (B): P.P., peristaltic pump; C_1, carrier solution; C_2, conditioning solution; D, detector; L, injection loop; R, coil; Q_1 and Q_2, flow rates; S, sample solution; W, waste; Position X, injection position; Position Y, loading position.

solutions, carried out by active components, as for example valves (T type) activated electrically.

The movement of the electrochemical cell between the two independent flow channels was obtained through its connection to the mobile part of the injector–commutator (Fig. 2B) by means of Teflon tubes (0.8-mm i.d.) with the shortest possible length. In position X of the injector–commutator, the sample was injected in the carrier solution (C_1) and led into the detector (D) where the measurement occurred, while in position Y the detector was positioned in a parallel channel, being crossed by the conditioning solution (C_2), which had a composition and flow rate independent from the carrying solution (C_1). Simultaneously with the regeneration of the working electrode a new filling of the injection loop (L) by the sample solution (S) occurred. The robust nature of the developed apparatus made up of the injector–commutator and the electrochemical cell of tubular configuration, permits the repositioning of the detector between the parallel channels without this movement acting as a source of instability. This is already demonstrated in FIA systems based on multi-site amperometric detection for the implementation of sequential or multiparametric determinations and using electrochemical cells of similar characteristics [31,32].

During its movement the detector remains in contact with a small amount of solution that flows in the channel where it initiated its movement, with the referred solution being rapidly drained when the detector is positioned in the other flow channel.

The study was initiated by carrying out the evaluation of the applied potential influence on the amplitude of the analytical signal obtained for diltiazem and nimesulide. Therefore, successive 50 µl injections were made of a diltiazem standard solution (3.0×10^{-5} M) or nimesulide (5.0×10^{-5} M) and the applied potential changed between 0.8 and 1.3 V. In both cases, an increase of the analytical signal with the increase in potential was obtained just to 1.1 V in the case of diltiazem and 1.2 V in the case of nimesulide. These values were selected for subsequent analysis.

The anodic response of diltiazem is attributed to the oxidation of the tertiary amine located in the side-chain of the molecule [21], whereas the anodic response of nimesulide could probably be attributed to the oxidation of the methylsulfonamide group contained in the structure of this compound [25].

By taking advantage of the concept of multi-site location of the detector, which permits the independent optimisation of the experimental conditions in the two flow channels, studies were carried out at this stage with a view to optimising the sample volume injected and the flow rate of the analytical channel. The volumes of sample injected in the flow system (20 and 100 µl) and the flow rates (0.8 and 3.0 ml min^{-1}) were optimised simultaneously, given their inter-dependence, with the values of 25 µl and 2.0 ml min^{-1} having been selected for the solutions of both drugs. The referred values gave rise to the attainment of a perfectly reproducible analytical signal. Lower

sample volumes affected the reproducibility of the results due to the mechanical limitations of the injector–commutator while higher volumes led to a very rapid deactivation of the working electrode surface.

With the previously selected parameters and with the detector in a fixed position (without the passage of a conditioning solution through the surface of the glassy carbon), the drugs solutions tested led to an increasing blockage of the glassy carbon electrode and, hence, progressive reduction of the electrode response. It was verified that the depression of the signal reached values of up to 40%, for a solution of diltiazem 2.5×10^{-4} M and 50% for a solution of nimesulide 3.0×10^{-4} M after 12 determinations (Fig. 3a).

The referred decrease in analytical signal could, however, be minimised if the detector was moved between the two flow channels. Given that in the FIA system with multi-site detector location, the electrochemical cell can be moved at any time, this was further explored with a view to reducing the contact time of the electrode surface with the sample plug. Indeed, the movement of the detector into the conditioning channel could be performed before the passage of the whole sample plug through the working electrode. In this way, the final portion of the plug did not reach the surface of the glassy carbon, being directly led into the drain. The study of the influence of the contact time of the detector with the sample plug on the degree of passivation produced was evaluated making the carrier solution pass in both flow channels and injecting the selected volume of sample (25 μl). In this study, it was decided to position the detector in the conditioning channel immediately after the maximum of the analytical signal. Such a procedure led on its own to a decrease in deactivation of the glassy carbon. For example, when successively injecting a solution of diltiazem 2.5×10^{-4} M, the decrease verified in the analytical signal after 12 measurements, which was about 40% when the detector operated in a fixed position (Fig. 3A-a), was only 30% when the sample plug was sectioned, after the peak reaches its maximum (Fig. 3A-b).

However, the decrease of electrode surface poisoning obtained due to the sectioning of the sample plug was by itself insufficient, for which reason an optimisation of not only the composition of the regenerator solution, but also its flow rate and the time necessary for regeneration, was carried out. This evaluation was concluded in an independent form for each of the two drugs.

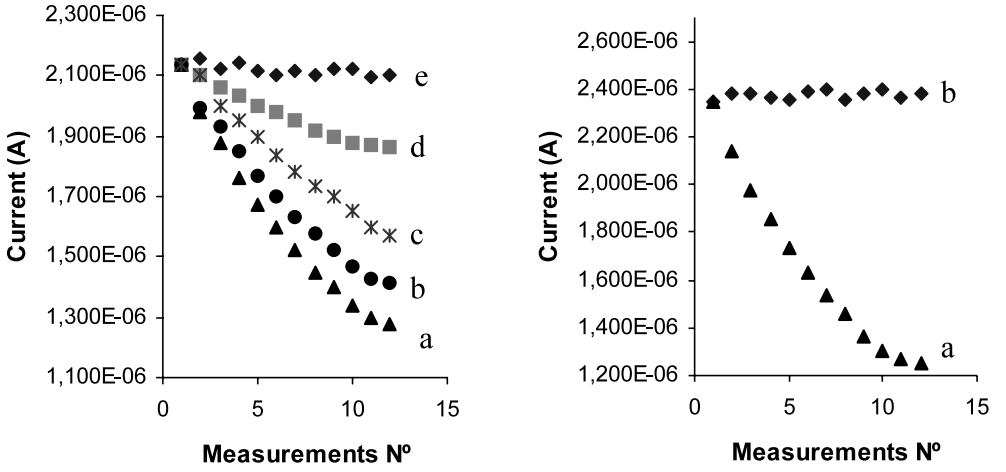

Fig. 3. (A) Response for a 2.5×10^{-4} M diltiazem solution when the detector operates in a static fashion (a); with relocation of the detector, but without conditioning (b) and with relocation of the detector and conditioning with a phosphate buffer solution (pH 7.4) (c); 0.1 M nitric acid solution (d) or with bi-deionised water (e); (B) Response for a 3.0×10^{-4} M nimesulide solution when the detector operates in a fixed position (a) and with relocation of the detector and conditioning of the glassy carbon with an ethanol/Britton–Robinson buffer mixture 70/30 (% v/v) at pH 6.1 (b).

The referred optimisation studies were carried out with a view to applying the flow manifolds to the analysis of diltiazem and nimesulide in pharmaceutical formulations. Therefore, the objective was to enlarge the upper limit of the linearity interval of the referred active compounds so that the corresponding formulations could be analysed without extensive dilutions.

All measurements made in the optimisation of the manifold and the determination of diltiazem and nimesulide in pharmaceutical formulations were repeated five times, unless otherwise stated.

3.1.1. Determination of diltiazem

The optimisation of the manifold parameters was initiated with the selection of the conditioner solution C_2 (Fig. 2) flowing in the parallel channel with a flow rate of approximately double that selected for channel C_1. This selection was made starting from a set of candidate solutions, which differ in pH, ionic strength and capacity to dissolve diltiazem and its reaction products. From the various solutions analysed, the solution that gave rise to a greater reproducibility of the measured analytical signal and simultaneously permitted a quicker return to the baseline was bi-deionised water. The most relevant results obtained in this optimisation stage are presented in Fig. 3A. It is possible to verify that by alternating each measurement of a diltiazem standard solution of concentration 2.5×10^{-4} M with the positioning of the electrochemical cell in the regeneration channel during the same time (≈ 40 s), the bi-deionised water ensured a stable response on the part of the working electrode (Fig. 3A-e) whereas with either the 0.1 M nitric acid solution (Fig. 3A-d) or the phosphate buffer solution (pH 7.4) (Fig. 3A-c), it gave rise to a decrease in the analytical response of approximately 10 and 25%, respectively. The bi-deionised water was used as a conditioning solution for subsequent studies.

One aspect necessary to take into account when choosing the conditioning solution deals with the fact that it should have a residual current not significantly different to that of the carrier solution. Indeed, when the detector is moved between the two flow channels it pulls in its interior, a small volume (130 μl) of the channel solution from where it moves. Therefore, when the detector returns from the conditioning channel to that of the measurement, a time interval is required so that the re-composition of the baseline occurs before the measurement of a new sample plug. This time interval is greater with the greater difference in the referred residual currents.

Once the residual currents that correspond to the bi-deionised water and carrier solution were different, it was necessary to evaluate the length of coil R (Fig. 2), positioned between the injection and detection points, to ensure that the necessary re-establishment of the baseline was obtained before a new sample plug reached the detector. Lengths of R falling between 30 and 120 cm were studied, with the value of 80 cm having been selected. Smaller reactors did not permit an efficient re-establishment of the baseline before the measurement of a new analytical signal, which compromised the reproducibility of the results, while larger reactors gave rise to a decrease in the analytical rate and a greater consumption of reagents. For the selected experimental conditions, the time necessary for an efficient re-establishment of the baseline was about 12 s.

With the objective of rapidly renewing the working electrode surface preparing it for a new measurement and compromising as little as possible the sampling rate, the minimum time of detector permanency in the conditioning channel and the regenerating solution flow rate were evaluated. Flow rate values between 1.8 and 4.0 ml min^{-1} were tested, having chosen a value of 3.5 ml min^{-1}, this being the greater flow rate tolerated by the physical characteristics of the injector–commutator, without causing excess pressures in the manifold which can caused random breakages of the connections between its diverse components.

Using a flow rate of 3.5 ml min^{-1}, it was shown that the detector permanency in the washing channel between each determination during 40 s was enough to allow the system to operate in a continuous form during a working day with a sampling rate greater than 50 determinations per hour.

Following the referred optimisation studies, successive injections of the diltiazem standard solutions with concentrations ranging from $5.0 \times$

10^{-5} to 2.5×10^{-4} M were carried out, obtaining a plot with a slope of 8167 μA/M, an intercept of −0.1056 μA, and a correlation coefficient of 0.9996 ($n = 6$).

The precision of the measurements, expressed as the relative standard deviation, was evaluated through successive injections of the more concentrated diltiazem standard solution (2.5×10^{-4} M). This was justified as an alternative to the utilisation of a solution with an intermediate concentration, since the possible irreproducibility of measurements arising from adsorption phenomena increase with the increasing concentration of the analyte. A value of 0.9% was obtained ($n = 12$).

The detection limit (signal to noise ratio = 3 [33]) was 8.7×10^{-7} M, which is a consequence of optimising the mounting for the determination of solutions with concentrations in the order of 0.1 mM. An optimisation of the manifold with the objective of quantifying trace quantities of diltiazem would give rise to the attainment of a value for the detection limit approximately 10 times lower, which would be of the same order of magnitude as that obtained by Wang and colleagues [21] in the determination of this active compound in pure aqueous solutions.

3.1.2. Determination of nimesulide

In the case of nimesulide the first choice of conditioning solution was ethanol, this being abandoned due to the large difference in value of residual current that corresponded to ethanol that flowed in channel C_2 and the carrier solution that flowed in C_1. Such a fact implied a long waiting time between determinations to wait for the restoration of the baseline, resulting in a significant decrease of the sampling rate.

As an alternative, several mixtures of Britton–Robinson buffer and ethanol were tested, having selected a mixture with 70% ethanol since it presented a good regenerating capacity (Fig. 3B) of the electrode surface, while not implying extended waiting times for the re-establishment of the baseline. With this conditioning solution, the coil length R, studied between 30 and 200 cm, was fixed at 100 cm.

In this way, when the detector was re-positioned in the measurement channel, the plug of the new sample injected took 35 s to reach the detector, this being the least time interval necessary to reach a baseline stable enough to allow a good analytical signal definition.

The flow rate of the conditioning solution, similar to that verified for diltiazem, was optimised at 3.5 ml min^{-1}. The permanency of the detector in the regeneration channel, evaluated between 15 and 60 s was fixed at 25 s. With all referred parameters optimised, the system operated continuously during the whole working day, allowing around 60 determinations per hour to be executed.

By intercalating several concentrations of nimesulide under the referred conditions, a linear relationship was obtained between those concentrations and the amplitude of the analytical signal in the interval 5.0×10^{-5} and 3.0×10^{-4} M (slope of 3010 μA/M, intercept of 0.011 μA and correlation coefficient of 0.9994, for $n = 6$). The reproducibility of the analytical signal was evaluated through 12 consecutive determinations of a 3.0×10^{-4} M solution with a relative standard deviation of 1.1% being attained.

The detection limit, calculated as previously referred [31], was 3.1×10^{-6} M.

3.2. Determination of diltiazem and nimesulide in pharmaceutical formulations

Following the optimisation of the manifold for each of the drugs, it was subsequently used in the quality control of pharmaceutical formulations common on the Portuguese market. Table 1 shows the results obtained in the determination of the diltiazem content. The agreement between the values obtained by the proposed and the reference procedures was assessed by the Student paired t-test in which the t-value calculated (0.78) was lower than the tabulated value (2.57) for a confidence level of 95% ($n = 6$). The relative deviations between both methods were always less than or equal to 1.5%.

The repeatability of the measurements was evaluated by carrying out 10 successive injections of a solution of Herbesser® formulation in which the concentration of diltiazem was about 1.5×10^{-4} M, with a R.S.D. of 1.2% being obtained.

Table 1
Assay of diltiazem in dosage forms by the proposed and the reference method

Pharmaceutical formulations	Amount found[a] (mg)		Relative error (%)
(tablets)	Proposed method	Reference method[b]	
Dilfar®	61.4±0.2	61.0±0.7	+0.6
Alandiem®	59.1±0.4	59.5±0.8	−0.6
Herbesser®	65.0±0.2	65.6±0.3	−0.8
Diltiazem Merck®	55.3±0.8	55.9±0.1	−1.1
Duplide®	91.6±1.8	90.5±0.5	+1.2
Etizem®	121.5±2.8	123.3±2.4	−1.5

[a] Average±S.D. of five determinations.
[b] USP XXIV.

Table 2
Assay and recovery of nimesulide in dosage forms

Pharmaceutical formulations (tablets)	Amount found[a] (mg)	Recovery[b] (%)
Aulin®	102.5±0.7	100.4±0.5
Donulide®	105.0±1.0	101.2±0.8
Jabasulide®	104.6±0.3	99.1±0.7
Nimed®	101.6±0.9	101.9±1.1
Sulimed®	98.0±0.6	102.8±0.4

[a] Average±S.D. of five determinations.
[b] Average of four determinations.

Regarding the determination of nimesulide (Table 2) the accuracy of the proposed FIA method was assessed by means of the spike recovery method. The mean value obtained was 101.1% with a R.S.D. of 0.7%.

The repeatability of the measurements was evaluated by carrying out 10 successive injections from a sample of Aulin® formulation in which the concentration of nimesulide was about 1.9×10^{-4} M, with a R.S.D. of 1.4% being obtained.

4. Conclusions

The FIA manifold with relocation of the voltammetric detection system whose capacity for the renewal of the working electrode surface is evaluated and commented on in this article, has proved to be a good strategy for the amperometric determination of pharmaceuticals that lead to a gradual loss of glassy carbon activity as it was demonstrated in the determination of both diltiazem and nimesulide. In both cases, the methodology developed revealed itself to be a good alternative to the processes of determination of these two active compounds in pharmaceutical formulations already described in the literature, given its ease of implementation, low cost and elevated rates of sampling attained (always greater than 50 samples per hour).

The versatility of the proposed methodology permits its easy adaptation to the quantification of these and other active compounds in other matrices, namely in biological fluids where they are present in trace quantities.

The possibility of the regeneration of the working characteristics of the glassy carbon electrodes allowed by its mobility in a flow system may constitute a contribution towards facilitating the out spread of electrochemical techniques in routine pharmaceutical analysis. This arises because it decreases the need for operator intervention, namely the preparation of the electrodes for each measurement, as frequently occurs in the determinations by batch procedures, as long as a tubular detection system with similar characteristics to those referred to in this work is available.

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