Piezoelectric pumping in flow analysis: Application to the spectrophotometric determination of gabapentin

Marta F.T. Ribeiro, João L.M. Santos*, José L.F.C. Lima

REQUIMTE, Faculdade de Farmácia da Universidade do Porto, Rua Aníbal Cunha 164, 4099-030 Porto, Portugal

ARTICLE INFO

Article history:
Received 13 October 2006
Received in revised form
10 November 2006
Accepted 14 November 2006
Published on line 19 November 2006

Keywords:
Piezoelectric micro-pump
Flow analysis
Pulsed flow
Gabapentin
1,2-Naphthoquinone-4-sulfonate
Multi-pumping

ABSTRACT

Solutions propelling devices are fundamental components of a flow-based analytical manifold. In this work different manifold configurations were implemented to evaluate the performance of multiple piezoelectric micro-pumps used as solutions insertion and propulsion devices. The micro-pumps are piezo-actuated micro-diaphragm pumps with passive check valves characterised by a small compact size and low power demands, and are able to produce reproducible flow rates of up to 4 mL min⁻¹. The flow rate is controlled by the frequency of the piezoelectric actuator (up to 20 Hz). As an additional feature, piezoelectric micro-pumps actuation generates a pulsed flowing stream that ensures a faster sample/reagent mixing contributing to improved reaction development.

The developed flow approach was assessed in the spectrophotometric determination of gabapentin in pharmaceutical preparations upon reaction with 1,2-naphthoquinone-4-sulfonate in alkaline medium. Distinct flow manifold configurations were designed for achievement of different solutions management. Linear calibrations plots for gabapentin concentrations of up to 150 mg L⁻¹, with relative standard deviations of less than 1.50% (n = 10) and a sample throughput of about 28 determinations per hour, were obtained.

© 2006 Elsevier B.V. All rights reserved.

1. Introduction

Since the appearance of flow injection analysis (FIA) [1], the need to adapt to new analytical requirements involving the number, diversity or quality of samples and results has motivated the continuous evolution of flow-based methodologies and the emergence of new techniques such as sequential injection analysis (SIA) [2], multicommutation [3] and more recently multi-pumping [4] flow systems (MPFS).

A fundamental component of the referred flow systems is the solutions propelling unit, given that it determines the characteristics of the flowing stream affecting solutions movement, sample/reagent mixing and therefore the delineation of the reaction zone. Peristaltic and syringe pumps are perhaps the two most widely used solution propulsion devices, being commonly employed in FIA, SIA and multicommutated systems. However, these units could present some shortcomings: peristaltic pumps are known to exhibit unpredictable fluctuations in flow rate due to the mechanism of propulsion and the loss of pump tubing elasticity, which has been minimised either by synchronisation devices [5] or by periodical tubing replacement; syringe pumps provide a more stable and consistent flowing stream, guaranteed by the reliability of the stepper-motor, although these systems are often less versatile, particularly when multiple solutions are used, and

* Corresponding author. Tel.: +351 22 2004427; fax: +351 22 2087132. E-mail address: joaolms@ff.up.pt (J.L.M. Santos).

0003-2670/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.aca.2006.11.035
require a periodical refilling that leads to lower sampling rates. Other propulsion alternatives such as electro-osmotic pumps [6] or gas pressurised systems [7] are scarcely used mostly in very specific situations. In recent years, solenoid micro-pumps used in MPFS [4] have exhibited and confirmed a great potential for application in flow-based automated analytical methodologies providing noteworthy advantages regarding more conventional solutions [8]. In MPFS, solenoid micro-pumps are the unique active components performing all the tasks (solutions insertions, propelling and commutation) that are typically assigned to distinct devices in the abovementioned flow techniques. Moreover, inherent to micro-pump actuation is a pulsed flow with hydrodynamic characteristics that contrasts with the laminar flow conditions associated with the utilisation of the previously referred propelling units. This promotes sample/reagent mixing contributing to a faster reaction zone homogenisation and to improved reaction development.

In this work piezoelectric micro-pumps are proposed as a new solutions propelling alternative. The micro-pumps are unidirectional, self-priming micro-diaphragm piezo-actuated devices, characterised by low power consumption and a great operational simplicity. They are also extremely light, low size compact units able to provide a reliable pumping of both liquids and gases at flow rates ranging from a few microliters to several milliliters per minute. Furthermore, the piezoelectric micro-pumps exhibit a very simple construction being made entirely of high precision microinjection moulded plastic components, which ensures high reliability and reproducibility and minimises the probability of failures or malfunctions. Their ability to handle very small volumes of fluids in an efficient and precise manner makes them ideal tools to implement miniaturised analytical systems. Similarly to solenoid micro-pumps, piezoelectric pumps actuation generates a pulsed flow with enhanced sample/reagent mixing capacity.

The performance and analytical potential of piezoelectric micro-pumps was evaluated in the development of a new automated methodology for the spectrophotometric determination of gabapentin in pharmaceutical preparations upon reaction with 1,2-naphthoquinone-4-sulfonate (NQS) in alkaline medium. This study involved the implementation and assay of flow manifolds of different configurations, comprising a variable number of micro-pumps, and their positioning at distinct locations in the analytical system.

Gabapentin [1-(aminomethyl)cyclohexaneacetic acid] is a new generation antiepileptic drug used for the treatment of partial seizures with or without secondary generalised tonic-clonic convulsions. Although gabapentin is an analogue of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, it is neither a GABA agonist nor antagonist and its mechanism of action is still unknown [9]. The importance of gabapentin has prompted the development of several methods for its determination mainly based on gas chromatography–mass spectrometry [10], liquid chromatography–mass spectrometry [11], high performance liquid chromatography [12–16] and capillary electrophoresis [17,18]. To our knowledge no spectrophotometric method and no flow-based procedure was developed for gabapentin determination.

2. Experimental

2.1. Reagents

All chemicals were of analytical reagent grade and doubly deionised water (conductivity < 0.1 µS cm$^{-1}$) was used throughout.

A 1.0 × 10$^{-3}$ mol L$^{-1}$ sodium 1,2-naphthoquinone-4-sulfonate (NQS) solution was prepared daily by weighing 0.026 g of NQS (Sigma) and dissolving in 100 mL of water. This solution was kept in an amber coloured flask to minimise exposure to light.

Gabapentin was kindly supplied by Tecnimede S.A., Portugal. A 500 mg L$^{-1}$ stock solution was prepared by dissolving 0.025 g of gabapentin in 50 mL of phosphate buffer (pH 10.3). Working standards within the 50–150 mg L$^{-1}$ range were daily prepared by suitable dilutions of the above stock with the phosphate buffer (pH 10.3).

Phosphate buffer solution pH 10.3 was prepared by dissolving 2.225 g of Na$_2$HPO$_4$ in 250 mL of water, and adjusting the pH with a 0.1 mol L$^{-1}$ NaOH solution.

Several pharmaceutical preparations commercially available in Portugal were analysed. For each preparation, 20 capsules or tablets were weighted and a mean content of a single formulation was estimated in order to prepare a 250 mg L$^{-1}$ gabapentin pharmaceutical stock solution. Working solutions were prepared by appropriate dilution. Spiked gabapentin solutions used in recovery studies were prepared by adding increasing amount of gabapentin in order to obtain gabapentin concentration values of 75, 100 and 150 mg L$^{-1}$.

2.2. Apparatus

Absorbance measurements (480 nm) were carried out in a Jenway 6300 spectrophotometer (Jenway, Dunmow, UK) equipped with a flow-cell (10 mm optical path, 18 µL inner volume).

The piezoelectric micro-pumps (MDP 1304, ThinXXS, Mainz, Germany) have the size of a small coin (26.2 mm of diameter, 7.5 mm of height, and a weight of 3 g) and need a 5 V power supply. The pumps are self-priming micro-diaphragm piezo-actuated: when voltage was applied the piezo-actuator moved up, the pump chamber expanded and the pressure difference induced the inlet valve to open (the pump chamber was filled). By dropping the applied voltage the piezo-actuator moved down, the inlet valve closed and the outlet valve opened. The fluid was pressed out, and the next pump cycle began (Fig. 1). An electronic pump control (EDP0604, ThinXXS, Mainz, Germany) was used to operate the piezoelectric micro-pumps by producing a peak voltage of −84/360 V. The electronic pump control was computer controlled by means of TTL signals for micro-pump actuation or switch off.

Flow rate of the propelled fluids was controlled by means of the frequency of the piezo-actuator, while fluid volumes were controlled by a time-based routine. The frequency was either manually or computer adjusted by using the internal frequency generator of the electronic pump control.

The flow set-up comprised a three-way solenoid valve 161T031 (NResearch Inc., West Caldwell, NJ, USA) operated by

The flow lines and reactors were made of PTFE tubing (0.8 mm i.d.). Homemade end-fittings and connectors were also used.

A Pentium I-based computer equipped with a PC-LABcard model PCL-711B (Advantech) interface card was used for the control of the piezoelectric micro-pumps and the solenoid valve by TTL signals. Software was developed in Microsoft Quick-Basic 4.5 and enabled as well data acquisition and processing [8].

2.3. Flow manifold

The developed flow manifold comprised one (Fig. 2A) or two piezoelectric actuated micro-diaphragm pumps (Fig. 2B) depending if the sample and reagent solutions were propelled through only one channel (aspiration mode) or if these solutions were individually delivered through dedicated channels (propulsion mode). In the former case, the single piezo-micro-pump was placed after the detector and both solutions were propelled by the micro-pump P (Fig. 2A), while in the latter the micro-pumps were placed before the solenoid valve, which acted as solutions merging point (Fig. 2B). In this configuration P2 was used to propel the sample solution and P1 to propel the reagent solution that was also the carrier stream. The three-way (two inlets, one outlet) normally closed solenoid valve V was used in both manifold configurations for selection of sample and reagent solutions. When V was switched off the NQS solution was inserted in the analytical path and when it was switched on it allowed the insertion of the sample solution.

The analytical cycle was similar in both manifolds and started by establishment of baseline by inserting the NQS solution, either by operating P (Fig. 2A) or P1 (Fig. 2B), at a fixed frequency which defined the flow rate during reagent/carrier insertion. During this phase V was switched off. By activating V and simultaneously operating P (Fig. 2A) or P2 (Fig. 2B) the sample was inserted in the analytical path during a predefined period of time (sampling time), which, in combination with the flow rate (defined by the micro-pump frequency actuation), determined the inserted sample volume. Subsequently, by operating P (Fig. 2A) or P1 (Fig. 2B) and simultaneously deactivating V, the NQS solution was introduced in the analytical system and the sample zone was carried out towards detection where it produced an analytical signal whose magnitude was proportional to the gabapentin concentration.

3. Results and discussion

As the main objective of this work was to explore the potentialities of the piezoelectric micro-pumps, two flow manifolds were designed and simultaneously evaluated in the spectrophotometric determination of gabapentin. The two flow configurations were very similar although they differ in fluids management: one of the manifolds had a simpler design comprising a unique piezoelectric micro-pump, which was used to propel all involved solutions in aspiration mode, therefore under negative pressure; the second manifold used a micro-pump for each of the individual solutions that were delivered in propulsion mode.

Several factors have been taken into consideration in the design of the flow manifolds, including not only the chemical parameters but also sample and reagent insertion times, solutions merging strategy, reaction time and flow rate. Since the implemented manifolds differed only on fluids management,
when comparing their performance a particular attention was given to the physical parameters. Effectively, it would be expected that the positioning of the micro-pumps at different places in the flow manifold would affect solutions propelling in different manners; for instance, in propulsion mode it would be more subject to backpressure effects, while in aspiration mode it would be more susceptible to air bubbles formation within tubing. In any case, these aspects and the functioning of the piezoelectric pumps in both circumstances would eventually affect a time-based control procedure whose performance depended markedly on temporised parameters (flow rate, sample volume, residence time, etc.).

### 3.1. Flow rate, reactor length and sampling time

A parameter with paramount influence in system performance, because it affected not only the sample volume but also the sample residence time, thus reaction development, was the flow rate. With the proposed piezoelectric micro-pumps the flow rate was defined by the frequency of pump actuation. For comparative purposes, flow rate was measured at the outlet port of the piezoelectric micro-pump (outlet micro-pump flow rate) and at the end of the developed flow manifolds after the detector (nominal flow rate) by using reactors with different lengths (0.5, 1.0 and 2.0 m) and different inner diameters (0.5, 0.8 and 1.5 mm). These assays were carried out by using water as the propelled fluid. The obtained results showed that the outlet micro-pump flow rate increased linearly with the frequency of pump actuation up to 20 Hz, which corresponds to an outlet flow rate of approximately 4 mL min$^{-1}$ (Fig. 3). Above this frequency, not only flow rate slightly decreases but precision is also markedly affected. At very high frequencies (above 80 Hz) the micro-pumps are damaged and their functioning became erratic.

At the end of the two flow manifolds (and for both propulsion modes), only a minor decrease in the nominal flow rate was observed, when compared with the outlet flow rate, by using tubing with an internal diameter (i.d.) of 1.5 mm. It should be emphasised that the i.d. of the micro-pump outlet port is 0.8 mm. By assaying reactors ranging from 0.5 to 2.0 m of length, at a 20 Hz actuation frequency a flow rate of 3.8 mL min$^{-1}$ (R.S.D. < 4.1%) was observed for all reactors.

The flow rate lessening was more pronounced for 0.8 and 0.5 mm i.d. tubing. However, and likewise what happened with 1.5 mm tubing, for 0.8 mm tubing the nominal flow rate was similar for all assayed reactor lengths (at a frequency of 20 Hz flow rate was 1.2 mL min$^{-1}$, R.S.D. < 3.0%). For 0.5 mm i.d. tubing flow rate markedly decreased as the reactor length increased, which was probably a consequence of the higher backpressure. With a reaction coil of 0.5 m the highest flow rate (0.81 mL min$^{-1}$) was attained at 15 Hz, while with 1.0 and 2.0 m reactors the highest flow rates (0.53 and 0.29 mL min$^{-1}$) were obtained at 10 and 5 Hz, respectively. For both reactors increasing the actuation frequency did not affect flow rate, which remained stabilised. In view of the obtained results 0.8 mm i.d. tubing was selected for the subsequent experiments.

After the preliminary evaluation of micro-pumps behaviour in terms of the relationship between frequencies of actuation, flow rate, tubing diameter and reactor length, the influence of the reagent/carrier flow rate during the determination of gabapentin was also investigated. By using frequencies of actuation between 2.5 and 20 Hz, which corresponded to flow rates of approximately 0.3–1.2 mL min$^{-1}$, comparable results were again obtained for both manifold configurations. These results showed that the analytical signal markedly decreased as the actuation frequency increased between 2.5 and 10 Hz (which corresponded to flow rates of approximately 0.3–0.86 mL min$^{-1}$) probably as a consequence of the decrease in the residence time that affected the available time for reaction development. Above 10 Hz it approached stabilisation. As a compromise between sensitivity and sampling rate, an actuation frequency of 5 Hz (corresponding to a flow rate of approximately 0.5 mL min$^{-1}$) was selected for the following experiments.

Influence of the reactor length was investigated in both manifolds by inserting a 100 mg L$^{-1}$ gabapentin solution by using a sampling time of 8 s, equivalent to a sample volume of 66.7 μL (flow rate of 0.5 mL min$^{-1}$), which was carried towards detection through different reactor lengths (0.5, 1.0, 1.5, 2.0 and 2.5 m). A similar behaviour was observed for both manifolds. The analytical signal markedly increased up to a 2.0 m reactor length and then approached stabilisation. Considering that the reactor length affected not only the analytical signal but also the sample throughput, as longer reactor lengths are associated with higher residence times, a reactor length of 1.5 m was selected for the experiments.

Sample volume is another important parameter that markedly affects the analytical system performance. With the proposed piezoelectric micro-pumps the sample volume is defined by the time used to operate the micro-pump during sample insertion (sampling time) and the flow rate. Evaluation of the sampling time was accomplished in both manifolds by using a 0.5 mL min$^{-1}$ flow rate and a 100 mg L$^{-1}$ gabapentin solution. This was inserted in the analytical path (1.5 m reactor length) either as a unique sample volume, which created two reaction interfaces, or by binary sampling (intercalation of multiple very small sample and reagent aliquots creating multiple reaction interfaces). The obtained results showed that the effect of the sampling time in the magnitude of the analytical signal was similar for both manifolds and for the two sampling strategies evaluated (Fig. 4). The analytical signal increased up to a sampling time of 8 s (which at a flow rate of 0.5 mL min$^{-1}$ corresponds to 66.7 μL of sample volume) and then approached stabilisation.

![Fig. 3 – Outlet micro-pump flow rate for distinct frequencies of actuation.](image-url)
An interesting feature regarding the utilisation of piezoelectric micro-pumps is that their actuation generates a pulsed flowing stream, similar to the one generated by solenoid micro-pumps [8], which is manifest in the small droplets of solution that the micro-pumps projected for each diaphragm movement (pulse). This pulsed flow has demonstrated in previous works [8,20] enhanced sample/reagent mixing capacity and hydrodynamic characteristics significantly different from the typical laminar flow conditions found in more conventional flow techniques. The only apparent difference, in terms of functioning, between solenoid and piezoelectric micro-pumps is that the former could be operated up to 5 Hz while the latter could be operated up to 20 Hz or even above, although both producing similar flow rates.

3.2. Chemical parameters

The influence of NQS reagent concentration was evaluated for concentrations ranging from $5 \times 10^{-5}$ to $2 \times 10^{-3}$ mol L$^{-1}$. The obtained results showed that the analytical signal markedly increased with the NQS concentration until $1 \times 10^{-3}$ mol L$^{-1}$, and then approached stabilisation. In view of the higher analytical signals obtained a $1 \times 10^{-3}$ mol L$^{-1}$ NQS solution was selected for the analysis.

Another chemical parameter affecting analytical signal magnitude was pH. It was verified that the reaction kinetics was favoured in alkaline medium and that a phosphate buffer solution at pH 10.3 provided the best results. At pH value above this value the linear working range was markedly reduced. Influence of buffer concentration was also studied at pH 10.3 for concentrations ranging from 0.01 to 0.1 mol L$^{-1}$.

The results showed a slight increase in the analytical signal up to 0.05 mol L$^{-1}$, after which it remained unchanged.

3.3. Analysis of pharmaceutical preparations

After optimisation, the developed flow systems were applied to the analysis of pharmaceutical preparations with the following operating parameters: 66.7 mL of sample corresponding to a sampling time of 8 s, inserted as a unique sample volume and transported towards detection through a 1.5 m reaction coil by using a $1 \times 10^{-3}$ mol L$^{-1}$ NQS solution, at a flow rate of 0.5 mL min$^{-1}$. Under these conditions linear calibrations plots for gabapentin concentrations up to 150 mg L$^{-1}$ were obtained in both configurations. The analytical curves were represented by $A = 0.0018C + 0.0039$ and $A = 0.0018C + 0.013$, for the flow systems working by aspiration and propulsion, respectively, where $A$ is the absorbance and $C$ is the gabapentin concen-

<table>
<thead>
<tr>
<th>Sample</th>
<th>Concentration added (mg L$^{-1}$)</th>
<th>Recovery$^a$ (mg L$^{-1}$)</th>
<th>Recovery$^a$ (%)</th>
<th>R.S.D. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurontin (600 mg, tablets)</td>
<td>25</td>
<td>25.9 ± 1.4</td>
<td>103.8 ± 5.6</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>78.4 ± 1.1</td>
<td>104.6 ± 1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Neurontin (800 mg, tablets)</td>
<td>25</td>
<td>26.4 ± 1.3</td>
<td>105.4 ± 5.3</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>76.9 ± 3.0</td>
<td>102.5 ± 4.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Generis (100 mg, capsules)</td>
<td>25</td>
<td>24.5 ± 1.5</td>
<td>97.9 ± 6.0</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>73.5 ± 1.9</td>
<td>98.1 ± 2.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Generis (400 mg, capsules)</td>
<td>25</td>
<td>24.2 ± 1.1</td>
<td>96.7 ± 4.3</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>72.9 ± 2.0</td>
<td>97.2 ± 2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Gabamox (300 mg, capsules)</td>
<td>25</td>
<td>24.2 ± 0.5</td>
<td>96.7 ± 2.0</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>71.2 ± 2.6</td>
<td>95.0 ± 3.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Merck (300 mg, capsules)</td>
<td>25</td>
<td>26.1 ± 1.3</td>
<td>104.4 ± 5.1</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>72.2 ± 0.7</td>
<td>96.3 ± 0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Bexal (400 mg, capsules)</td>
<td>25</td>
<td>25.4 ± 1.3</td>
<td>101.8 ± 5.0</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>71.1 ± 1.8</td>
<td>97.8 ± 2.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Ciclum (400 mg, capsules)</td>
<td>25</td>
<td>26.4 ± 1.2</td>
<td>105.6 ± 4.6</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>71.4 ± 1.6</td>
<td>95.2 ± 2.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

$^a$ Mean ± S.D. (n = 6).
by using the regression equation (with \( Y \)) 6 months.

The interfering effect of several compounds commonly used as excipients in capsules and tablets formulations was also assessed. One hundred milligrams per liter gabapentin standard solutions containing increasing amounts of the excipients were analysed in the developed systems. A composite solution containing increasing amounts of the excipients was considered as interfering if the analytical signal variation was ±5% regarding the one obtained in its absence. It was verified that up to 80 molar ratio excipient/gabapentin compounds such as galactose, lactose, sucrose, t alc, cornstarch and magnesium stearate did not interfere.

Since there is no available reference methodology for gabapentin determination the developed systems were evaluated by carrying out recovery studies. Two distinct amounts of gabapentin (25 and 75 mg L\(^{-1}\)) were added to solutions of several gabapentin pharmaceutical formulations. The obtained results (Tables 1 and 2) showed recovery values, in percentage, between 94.8 and 105.6, which further confirm the absence of interfering matrix effects.

For both systems sampling rate was about 28 determinations per hour with a sample and reagent consumption of 66.7 \( \mu \)L and 0.26 mg, respectively, per determination. No baseline drift was observed. The piezoelectric micro-pumps functioning remained unaltered throughout the procedure implementation and assessment (approximately 6 months).

### Table 2 – Recovery values for gabapentin pharmaceutical preparations by using the flow manifold involving the utilisation of two piezoelectric micro-pumps (propulsion mode)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Concentration added (mg L(^{-1}))</th>
<th>Recovery(^a) (mg L(^{-1}))</th>
<th>Recovery(^a) (%)</th>
<th>R.S.D. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurontin (600 mg, tablets)</td>
<td>25</td>
<td>26.3 ± 1.2</td>
<td>105.3 ± 4.7</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>76.4 ± 1.6</td>
<td>101.9 ± 2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Neurontin (800 mg, tablets)</td>
<td>25</td>
<td>25.9 ± 1.2</td>
<td>103.5 ± 4.7</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>71.2 ± 2.2</td>
<td>94.9 ± 3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Generis (100 mg, capsules)</td>
<td>25</td>
<td>24.6 ± 1.3</td>
<td>98.3 ± 5.0</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>75.3 ± 3.2</td>
<td>100.4 ± 4.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Generis (400 mg, capsules)</td>
<td>25</td>
<td>24.8 ± 1.2</td>
<td>99.3 ± 4.8</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>77.8 ± 1.6</td>
<td>103.7 ± 2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Gabamox (300 mg, capsules)</td>
<td>25</td>
<td>26.0 ± 1.3</td>
<td>104.0 ± 5.4</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>73.1 ± 3.5</td>
<td>97.5 ± 4.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Merck (300 mg, capsules)</td>
<td>25</td>
<td>24.4 ± 1.2</td>
<td>97.5 ± 4.8</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>71.8 ± 2.7</td>
<td>95.7 ± 3.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Bexal (400 mg, capsules)</td>
<td>25</td>
<td>25.7 ± 1.0</td>
<td>102.6 ± 3.9</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>72.7 ± 3.4</td>
<td>97.0 ± 4.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Ciclum (400 mg, capsules)</td>
<td>25</td>
<td>26.3 ± 1.0</td>
<td>105.2 ± 4.1</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>76.0 ± 3.8</td>
<td>101.3 ± 5.1</td>
<td>5.0</td>
</tr>
</tbody>
</table>

\(^a\) Mean ± S.D. (n = 10).

### 4. Conclusions

The obtained results confirmed the analytical potential of piezoelectric micro-pumps for the implementation of automated flow-based analytical methodologies. As most relevant features of these devices one should emphasise the small dimensions, low-cost, compactness and simplicity of construction that enable the development of low size, reliable and easily maintained flow systems; the high degree of automation they provide, since the most important analytical parameters are computer controlled, facilitating system operation and monitoring; the high flexibility and versatility, taking into consideration the distinct solutions manipulations they permit and the ease of adaptation to distinct analytical situations; the pulsed nature of the flow, which enabled the propulsion of the involved solutions under improved mixing conditions. These advantageous characteristics make piezoelectric micro-pumps a valuable alternative to the more conventional propulsion devices used in flow analysis.

The methodologies developed for gabapentin determination, either by using a specific piezoelectric micro-pump for each solution (propulsion mode) or by using a single micro-pump for all solutions (aspiration mode), are valuable strategies for the determination of this drug in pharmaceutical preparations and can be considered advantageous alternatives to other available procedures due to their simplicity, promptness, precision, accuracy, low reagent consumption and low waste generation. Furthermore, they use very accessible equipment and do not require skilful operators.

### Acknowledgments

One of us (M.F.T. Ribeiro) thanks FCT and FSE (III Quadro Comunitário de Apoio) the Ph.D. grant (BD/10400/2002).
REFERENCES