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Universidade Estadual Paulista Júlio de
Mesquita Filho
Brasil

Fatibello-Filho, O.; Vieira, H. J.

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Spectrophotometric flow injection procedure to indirect determination of paracetamol in pharmaceutical formulations using o-tolidine as reagent

O. Fatibello-Filho, H. J. Vieira*

*Departamento de Química, Centro de Ciências Exatas e de Tecnologia
Universidade Federal de São Carlos, São Carlos, Brasil.*

**bello@dq.ufscar.br*

Abstract: A spectrophotometric flow injection method for the determination of paracetamol in pharmaceutical formulations is proposed. The procedure was based on the oxidation of paracetamol by sodium hypochloride and the determination of the excess of this oxidant using *o*-tolidine dichloride as chromogenic reagent at 430 nm. The analytical curve was linear in the paracetamol concentration range from 8.50×10^{-6} to 2.51×10^{-4} mol L⁻¹ with a detection limit of 5.0×10^{-6} mol L⁻¹. The relative standard deviation was smaller than 1.2% for 1.20×10^{-4} mol L⁻¹ paracetamol solution ($n = 10$). The results obtained for paracetamol in pharmaceutical formulations using the proposed flow injection method and those obtained using a USP Pharmacopoeia method are in agreement at the 95% confidence level.

Keywords: paracetamol; pharmaceutical analysis; flow injection analysis; spectrophotometry.

Introduction

Paracetamol (4-acetoaminophen) has mild analgesic and antipyretic properties and is, along with acetylsalicylic acid, one of the most popular analgesic agents. The administration of this drug with caffeine yields analgesic effects significantly greater than that of paracetamol alone [1, 2].

Several methods have been employed for the spectrophotometric determination of this drug in combined dosage forms [3-7]. Chromatographic methods have been proposed for the simultaneous determination of paracetamol and other active principles [8-10]. Fluorescence spectroscopy methods were also described [11, 12], however those methods are time-consuming and use expensive equipments. Electroanalytical methods were proposed to paracetamol determi-

nation in pharmaceutical formulations using carbon paste electrode [13-15].

Flow injection systems are useful tools for the automation, miniaturization and simplification of analytical processes. These procedures permit obtain results faster and accurate than batch procedures [16].

Flow injection spectrophotometric systems with spectrophotometric detection were described using nitrite as reactant [17-19]. Other spectrophotometric flow injection methods based on reaction of paracetamol to produce a indophenol dye [20-24] and systems with solid phase UV spectrophotometric detection [25-28] have been described for paracetamol determination in pharmaceutical formulations. Flow procedures with chemiluminescence detection were described using luminol based reaction [29, 30]

and another method employed the oxidation of tris(2,2'-bipyridyl)ruthenium(II) by potassium permanganate [31]. A Fourier transformed infrared (FTIR) method based on the detection of products formed in the alkaline hydrolysis of paracetamol was also proposed in the literature [32]. A flow-injection method with spectrofluorimetric detection to determine paracetamol based on its oxidation with hexacyanoferrate(III) was reported [33]. Different techniques for quantification of paracetamol in pharmaceuticals were evaluated in a recent review [34].

The major substances found as products of chlorination of paracetamol were 1,4-benzoquinone and N-acetyl-p-benzoquinoneimine (NAPQI). Other products that were identified included the chloro-4-acetamidophenol and dichloro-4-acetamidopheno [35].

In this article a fast, simple and accurate flow injection procedure with spectrophotometric detection to determine paracetamol in pharmaceutical products exploiting the reaction between paracetamol and hypochlorite is proposed. In this method the excess of oxidant was determined spectrophotometrically using *o*-tolidine (3,3'-dimethylbenzidine) as reagent at a wavelength of 430 nm.

Experimental

Reagents and solutions

All experiments were performed with chemicals of analytical grade: paracetamol (Sigma), *o*-tolidine hydrochloride (Merck), sodium hypochlorite (Vetec, São Paulo, Brazil) and sodium borate (Synth), were used as received. All solutions were prepared with desionized water from a Millipore (Bedford, MA) Milli-Q system (model UV Plus Ultra-Low Organics Water).

A 8.53×10^{-3} mol L⁻¹ paracetamol stock solution was prepared dissolving 129 mg of this drug with desionized water in a 100.0 mL calibrated flask and reference solutions were prepared by appropriate stock solution dilution with desionized water.

A 4.31×10^{-3} mol L⁻¹ *o*-tolidine dichloride (3,3'-Dimethyl-(1,1'-biphenyl)-4,4'-diamine) stock solution was prepared dissolving 123.0 mg of the reagent with desionized water in a 100.0

mL calibrated flask. An additional dilution was performed in 250.0 mL calibrated flask with 0.19 mol L⁻¹ HCl solution to obtain a 9.8×10^{-5} mol L⁻¹ *o*-tolidine work solution.

A sodium hypochlorite stock solution was prepared diluting 2.0 mL of the concentrated solution in a 250.0 mL calibrated flask with a 1.00×10^{-2} mol L⁻¹ borate buffer solution (pH 9.0). An additional dilution was performed transferring 2.0 mL of this solution to a 250.0 mL calibrated flask and the volume was made up with a 1.00×10^{-2} mol L⁻¹ borate buffer solution. This stock solution was standardized using a titrimetric method.

A 0.19 mol L⁻¹ HCl solution was prepared by dilution of 8.0 mL HCl (Merck) in 500.0 mL and this solution was standardized with a 0.100 mol L⁻¹ NaOH standard solution.

Brazilian pharmaceutical products such as, Cibalena® (Novartis Indústria Farmacêutica, S.B. dos Campos, SP); Tylenol 500®, Tylenol 750® and Tylenol DC® (Janssen-Cilag Farmacêutica, São José dos Campos, SP); Tyramol 750® (Laboratórios Farmacêuticos Caresse, São Paulo); Paracetamol 500® (EMS Sigma Pharma, Hortolândia, São Paulo); Resfry® (Laboratório Neo Química Com. Ind. Ltda, Anápolis, GO); Paracetamol® (Eurofarma Laboratórios Ltda, São Paulo) were purchased from a local drugstore and analyzed using the proposed flow method and a comparative USP Pharmacopoeial procedure [36].

Apparatus

Flow injection spectrophotometric measurements were carried out using a Femto 485 spectrophotometer (São Paulo, Brazil) equipped with a Hellma® flow cell (path length 10 mm, inner volume 18 µL, NY, USA) connected to a Cole-Parmer (Chicago, IL, USA) model 1202-0000 two-channel strip-chart recorder. An Ismatec® IPC-12 peristaltic pump (Zurich, Switzerland) supplied with Tygon® tubing and an injector-commutator were used throughout [37]. The flow manifold was constructed with polyethylene tubing (0.8 mm i.d.).

Preparation of pharmaceutical samples

The contents of tablets or sachets were weighed and powered in a mortar. Mass varying from 120.0 to 156.0 mg of paracetamol were accurately weighed and dissolved with 30 mL of

desionized water in 50.0 mL calibrated flask. These solutions were gently shaken by 10 min and the volume was completed with desionized water. Another dilution from theses solutions were performed using aliquots varying from 195-200 μL to obtain final concentrations of *ca.* $1.10 \times 10^{-4} \text{ mol L}^{-1}$ in 25.0 mL calibrated flask with desionized water.

For the liquid formulation, an accurate aliquot of 200 μL was transferred to a 50.0 mL calibrated flask and the volume was completed with desionized water. The final concentration obtained was *ca.* $1.1 \times 10^{-4} \text{ mol L}^{-1}$.

Flow injection procedure

In the flow injection manifold, shown in the Figure 1, when the all solutions were propelled by peristaltic pump, a baseline was generated by reaction between the sodium hypochlorite and the *o*-tolidine streams and continuously monitored by spectrophotometer at 430 nm (equation 1, Scheme 1). The sample or standard solutions containing paracetamol (80 cm; 400 μL) were injected with the aid of injector-commutator into desionized carrier stream (C; 2.2 mL min^{-1}) and merges downstream with $9.4 \times 10^{-5} \text{ mol L}^{-1}$ hypochlorite solution in $1.00 \times 10^{-2} \text{ mol L}^{-1}$ borate buffer solution (pH 9.0) (R_1 ; 0.9 mL min^{-1}) in the confluence point X promoting the consumption of ClO^- (equation 2, Scheme 1). After the reaction coil RC_1 (75 cm), the dispersed sample zone merges with a colorless $9.8 \times 10^{-5} \text{ mol L}^{-1}$ *o*-tolidine solution in 0.20 mol L^{-1} HCl solution at confluence point Y (R_2 ; 1.6 mL min^{-1}) where the yellow reaction product was monitored spectrophotometrically. In this way, the decrease of absorbance (ΔA) caused by hypochlo-

rite consumption was proportional to concentration of paracetamol in the solution injected.

Comparative procedure

To validation of proposed flow injection method the results obtained were compared with those results obtained using a comparative USP Pharmacopoeia procedure [36]. This procedure is based in the intrinsic absorption of paracetamol in UV region ($\lambda = 244 \text{ nm}$). For the determination of paracetamol, the samples and reference solutions were diluted in sodium hydroxide solution and the concentration of paracetamol was performed by interpolation in an analytical curve.

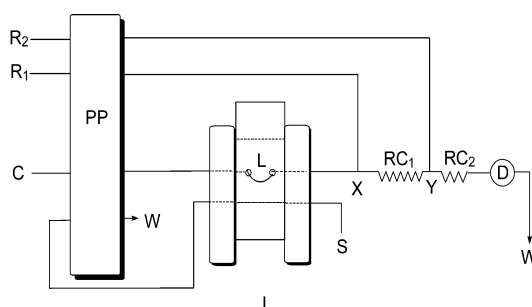
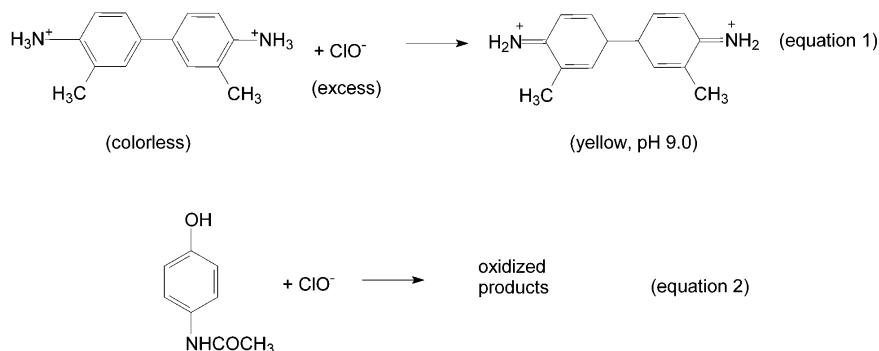


Figure 1. Flow injection spectrophotometric method for paracetamol determination in pharmaceutical products. PP: peristaltic pump; L: sample loop (400 μL); C: carrier (H_2O ; 2.2 mL min^{-1}); R_1 : $9.4 \times 10^{-5} \text{ mol L}^{-1}$ hypochlorite solution (0.9 mL min^{-1}); R_2 : $9.8 \times 10^{-5} \text{ mol L}^{-1}$ *o*-tolidine solution (1.6 mL min^{-1}); I: injector-commutator (80 cm; 400 μL); RC_1 and RC_2 : reaction coil (75 cm, both); D: spectrophotometer ($\lambda = 430 \text{ nm}$); X and Y: confluence point and W: waste. The distance between the injector I and X confluence point was 5 cm.



Scheme 1.

Results and discussions

Paracetamol exhibited significant reactivity with hypochlorite when exposed in large molar excess, leading to the production of multiple products such as 1,4-benzoquinone, N-acetyl-p-benzoquinoneimine and another products with molar mass higher than 300 g mol^{-1} [12, 35].

The proposed flow injection system is based on the ability of oxidation of paracetamol by hypochlorite in excess at pH 9.0 and the hypochlorite excess was monitored with *o*-tolidine producing a yellow diiminequinone at pH 9.0 [12, 38].

The chemical and flow injection parameters were optimized by univariate method in order to achieve a good compromise between the peak height, reproducibility, accuracy, precision, baseline stability and analytical frequency.

Chemical parameters

Preliminary studies to optimize chemical parameters were carried out using a manifold shown in Figure 1. In this flow system the hypochlorite and *o*-tolidine flow rates was 1.2 mL min^{-1} and that of carrier was 2.2 mL min^{-1} , the sample loop of $100 \mu\text{L}$, reaction coil length RC_1 of 150 cm and reaction coil length RC_2 of 60 cm were also used. Initially, the effect of hypochlorite concentration over the range from 2.4×10^{-5} to $1.2 \times 10^{-4} \text{ mol L}^{-1}$ on the analytical signal (ΔA) for a $9.4 \times 10^{-5} \text{ mol L}^{-1}$ paracetamol solution, using a $9.8 \times 10^{-5} \text{ mol L}^{-1}$ *o*-tolidine in 0.22 mol L^{-1} HCl solution was investigated. The analytical signal increased with increase of hypochlorite concentration up to $9.4 \times 10^{-5} \text{ mol L}^{-1}$ and, remaining constant for higher concentrations. Thus, a $9.4 \times 10^{-5} \text{ mol L}^{-1}$ hypochlorite solution was selected in further work.

The effect of HCl concentration in the *o*-tolidine solution on the peak high was studied from 4.4×10^{-2} to 0.22 mol L^{-1} using a $9.4 \times 10^{-5} \text{ mol L}^{-1}$ hypochlorite solution and $9.8 \times 10^{-5} \text{ mol L}^{-1}$ *o*-tolidine solution. The analytical signal increased with increase of the HCl concentration up to 0.20 mol L^{-1} and remaining constant for higher concentrations. Thus, the 0.20 mol L^{-1} HCl was selected for further work.

To study the effect of pH of hypochlorite solution, a $1.00 \times 10^{-2} \text{ mol L}^{-1}$ borate buffer solution was employed. The study was performed over the

pH range from 7.0 to 11.4. The analytical signal showed a slight increased with increase of pH up to pH 9.0. Higher pH promotes a severe interfere in the reaction between ClO^- and *o*-tolidine decreasing the analytical signal due the consumption of HCl of the stream before the confluence point.

The effect of *o*-tolidine concentration on the analytical signal was investigated in the concentration range from 1.6×10^{-5} to $1.2 \times 10^{-4} \text{ mol L}^{-1}$. It was observed that the analytical signal increased with the increases of *o*-tolidine concentration up to $9.8 \times 10^{-5} \text{ mol L}^{-1}$ remaining constant for higher *o*-tolidine concentrations. Furthermore, a 9.8×10^{-5} *o*-tolidine solution was selected for further studies.

Flow injection parameters

The effect of the coiled reactor (RC_1 and RC_2) length on the analytical signal was studied from 30 to 150 cm. In this study, it was observed that increasing the length of coiled reactor RC_1 up to 75 cm promote a slight increase of analytical signal. For higher coiled reactor length the analytical signal decreased. Therefore, a 75 cm reactor length (RC_1) was selected. The effect of reactor coil RC_2 length was studied over the same range, the signal showed best peak height using a 75 cm length. A reactor coil RC_2 of 75 cm length was selected to further experiments.

The effect of sample volume from 100 to $600 \mu\text{L}$ on peak height (ΔA) was studied for a $5.8 \times 10^{-4} \text{ mol L}^{-1}$ paracetamol reference solution. The analytical signal increased with increase of sample loop volume. Considering the repeatability and height of analytical signal, a $400 \mu\text{L}$ sample loop length was selected.

The effect of flow rate for *o*-tolidine, hypochlorite and carrier (desionized water) on analytical signal was studied in the flow rates of 0.9, 1.6 and 2.2 mL min^{-1} , respectively. It was found that the analytical signal decreased deeply with the increasing of hypochlorite flow rate (R_1). Therefore, a flow rate of 0.9 mL min^{-1} was selected for further experiments. In the *o*-tolidine flow rate (R_2) study it was observed that the highest analytical signals were obtained for the 1.6 mL min^{-1} flow rate. This flow rate was selected as optimum. In the study of effect of carrier flow rate on the analytical signal showed that the flow rate of 2.2 mL

min⁻¹ promotes the best analytical signal in terms of sensitivity and analytical frequency. Thus, a flow rate of 2.2 mL min⁻¹ was selected in this work.

Interferences and recovery studies

The selectivity of the proposed flow injection procedure was studied comparing the analytical signal of a 1.5×10^{-4} mol L⁻¹ paracetamol standard solution with 1.5×10^{-4} mol L⁻¹ paracetamol reference solutions containing the commonly excipients found in commercial pharmaceutical formulations in the concentrations that cause a error of $\pm 5\%$. The studied excipients were

Table 1. Recoveries of paracetamol standard solutions.

Samples	Added / 10 ⁻⁴ mol L ⁻¹	Founded / 10 ⁻⁴ mol L ⁻¹	Recovery / %
Cibalena®	0.50	0.50	100
	0.95	0.96	101
	1.12	1.13	101
Tylenol 500®	0.50	0.50	100
	0.95	0.93	97.8
	1.12	1.09	97.3
Tyramol 750®	0.50	0.51	102
	0.95	0.97	102
	1.12	1.10	98.2
Tylenol 750®	0.50	0.52	104
	0.95	0.97	102
	1.12	1.11	99.1
Paracetamol 500®	0.50	0.50	100
	0.95	0.97	102
	1.12	1.15	103
Tylenol DC®	0.50	0.50	100
	0.95	0.94	98.9
	1.12	1.10	98.2
Resfry®	0.50	0.50	100
	0.95	0.94	98.9
	1.12	1.10	98.2
Paracetamol®	0.50	0.49	98.0
	0.95	0.94	98.9
	1.12	1.11	99.1

n=3.

polivinylpirrolidone, citric acid, saccharine, tartrazine, caffeine, EDTA and sodium carboxymethylcellulose. Only the citric acid and caffeine showed high interference above an analyte:interference ratio of 1:10. Probably, these substances are oxidized by ClO⁻. But, the amounts of these substances in the commercial pharmaceuticals are lower than that of paracetamol. The other excipients do not shown any interference at the same concentration of paracetamol.

The study of addition and recovery of paracetamol in pharmaceutical products was performed to verify the interference in potential of sample matrix. Tablets and syrups were employed. This study was performed spiking three aliquots of paracetamol standard solution in the concentrations of 5.00×10^{-5} ; 9.50×10^{-5} and 1.10×10^{-4} mol L⁻¹ in a sample solution containing 1.12×10^{-4} mol L⁻¹ paracetamol. Recoveries of paracetamol ranged from 97.3 to 103% as shown in Table 1. These results obtained suggested an absence of matrix effect on those determinations.

Analytical features and application

The flow injection procedure developed present an analytical curve linear in the paracetamol concentration range from 8.50×10^{-6} to 2.51×10^{-4} mol L⁻¹ described by equation: $\Delta A = 0.058 + 1.571,41 \times C$; $r = 0.9990$, where ΔA is ($A_1 - A_2$), the difference between the baseline absorbance (A_1) and the transient signal of solution injected containing paracetamol, and C is the paracetamol concentration in mol L⁻¹.

The relative standard deviation (RSD) was lower than 1.2% ($n = 10$) for 1.20×10^{-4} mol L⁻¹ paracetamol solution and the detection limit obtained was 5.0×10^{-6} mol L⁻¹ (three times blank signal/inclination of analytical curve). The analytical frequency of 60 determinations per hour was obtained.

The paracetamol determination was performed using the developed spectrophotometric flow injection method and the results obtained were compared with those obtained using a USP Pharmacopoeia procedure [36]. As shown in Table 2, the results obtained using the proposed flow injection procedure are in good agreement with those results obtained using the comparative procedure at confidence level of 95%.

Analytical features attained by the proposed flow procedure and those reported by described flow procedures with spectrophotometric detection are presented in Table 3. The linear response was comparable with flow system where paracetamol was hydrolyzed before the detection [39] and higher than system described where paracetamol is monitored at an optode [18, 27]. The procedure proposed by Knochen et al. [17] uses a second degree polynomial analytical curve. The sampling rate was higher than procedures that have used alkaline hydrolysis and optode as sensor. The detection limit was better than previously reported by Burakham et al. [18],

but compare unfavorably with those obtained by Criado et al. [39] and by Cañada et al. [27]. However, these flow procedures have showed lower sampling rate.

The proposed flow system compare favorably with a chemiluminescence flow procedures described by Alapont et al. [29] and by Pulgarin and Bermejo [33], showing better precision and largest linear range.

Conclusions

The proposed flow procedure was suitable for the determination of paracetamol in pharmaceutical formulations, presenting accuracy and precision necessary to quality control laboratories. The paracetamol determination not requires extensive preliminary sample treatment. The procedure does not require expensive reagents and can be implemented easily in pharmaceutical laboratories. This procedure is simpler than spectrofluorimetric procedure described by Vilchez et al. [12] due the use of a suitable spectrophotometer.

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Table 2. Determination of paracetamol in pharmaceutical products using the flow injection and the USP procedure [36].

Samples	Paracetamol/mg g ⁻¹		Relative error (Er / %)
	USP	Proposed	
Cibalena®	300 ± 5	302 ± 3	0.7
Tylenol 500®	850 ± 4	840 ± 4	-1.2
Tyramol 750®	860 ± 6	820 ± 3	-4.6
Tylenol 750®	850 ± 7	861 ± 4	1.3
Paracetamol 500®	820 ± 4	868 ± 3	5.8
Tylenol DC®	760 ± 6	771 ± 2	1.4
Resfry®	410 ± 5	391 ± 1	-4.6
Paracetamol®(*)	198 ± 6	203 ± 2	2.5

n=3;

(*)mg L⁻¹;

Er: FIA vs. USP procedure.

Table 3. Analytical features of spectrophotometric flow procedures for paracetamol determination in pharmaceuticals.

	[17]	[18]	[27]	[39]	Proposed
Linearity/ 10 ⁻⁴ mol L ⁻¹	1.2 to 198	26.4 to 66.1	0.03 to 0.5	0.04 to 1.3	0.085 to 2.5
		or 66.1 to 165			
RSD/% (mol L ⁻¹)	< 1.3	2 (1.3x10 ⁻²)	1.24 (2.6x10 ⁻⁵)	1.8 (2.6x10 ⁻⁵)	1.2 (1.2x10 ⁻⁴)
Detection limit/ 10 ⁻⁵ mol L ⁻¹	^a	29.7	1.45x10 ⁻²	0.13	0.5
Analytical frequency	120	60	40	20	60

^a not reported.

O. F. Filho, H. J. Vieira. Método de análise por injeção em fluxo para determinação indireta de paracetamol em formulações farmacêuticas empregando o-tolidina como reagente.

Resumo: Um procedimento de injeção em fluxo com detecção espectrofotométrica para a determinação de paracetamol foi descrito. O procedimento foi baseado na reação de oxidação do paracetamol pelo hipoclorito de sódio e a determinação de seu excesso empregando o dicloreto de o-tolidina como reagente cromogênico. A curva analítica apresentou um comportamento linear entre as concentrações de paracetamol de $8,5 \times 10^{-6}$ a $2,51 \times 10^{-4}$ mol L⁻¹ com um limite de detecção de $5,0 \times 10^{-6}$ mol L⁻¹. O desvio padrão relativo foi menor que 1,2% para uma solução de paracetamol de $1,20 \times 10^{-4}$ mol L⁻¹ (n=10). Os resultados obtidos nas análises de produtos farmacêuticos comerciais obtidos empregando o procedimento desenvolvido foram comparados com aqueles obtidos empregando o procedimento descrito na Farmacopéia Americana (USP XXII) estando em concordância ao nível de confiança de 95%.

Palavras-chave: Paracetamol; produtos farmacêuticos; análise por injeção em fluxo; espectrofotometria.

References

- [1] L.S. Goodman, A. Gilman, Bases Farmacológicas de la Terapêutica, 4 edition, New York, Interamericana, 1974.
- [2] F.D. Fuchs, L. Wannmacher, Farmacologia Clínica - Fundamentos da Terapêutica Racional, 2 ed., Rio de Janeiro, Guanabara Koogan, 1999.
- [3] E. Dinc, C. Yucesoy, F. Onur, J. Pharm. Biomed. Anal. 28 (2002) 1091.
- [4] S.D. Cekic, H. Filik, R. Apak, J. Anal. Chem. 60 (2005) 1019.
- [5] A. Afkhami, N. Sarlak, Acta Chim. Slov. 52 (2005) 98.
- [6] P. Nagaraja, K.C.S. Murthy, K.S. Rangappa, J. Pharm. Biomed. Anal. 17 (1998) 501.
- [7] J.S.E. Romero, L.A. Rodriguez, M.C.G. Alvarezcoque, G. Ramisramos, Analyst 119 (1994) 1381.
- [8] R.N. Rao, A. Narasaraaju, Anal. Sci. 22 (2006) 287.
- [9] L. Monser, F. Darghouth, J. Pharm. Biomed. Anal. 27 (2002) 851.
- [10] M. Gil-Agusti, L. Monferrer-Pons, M.C. Garcia-Alvarezcoque, J. Esteve-Romero, Talanta 54 (2001) 621.
- [11] A.B. Moreira, H.P.M. Oliveira, T.D.Z. Atvars, I.L.T. Dias, G.O. Neto, E.A.G. Zagatto, L.T. Kubota, Anal. Chim. Acta 539 (2005) 257.
- [12] J.L. Vilchez, R. Blanc, R. Avidad, A. Navalon, J. Pharm. Biomed. Anal. 13 (1995) 1119.
- [13] I.C. Vieira, K.O. Lupetti, O. Fatibello-Filho, Quim. Nova 26 (2003) 39.
- [14] C.Y. Wang, X.Y. Hu, Z.Z. Leng, G.J. Yang, G.D. Jin, Anal. Lett. 34 (2001) 2747.
- [15] O. Fatibello-Filho, K.O. Lupetti, I.C. Vieira, Talanta 55 (2001) 685.
- [16] J. Martínez-Calatayud, Flow Injection Analysis of Pharmaceuticals - Automation in Laboratory, 1 ed., Taylor & Francis Inc., 1996.
- [17] M. Knochen, J. Giglio, B.F. Reis, J. Pharm. Biomed. Anal. 33 (2003) 191.
- [18] R. Burakham, S. Duangthong, L. Patimaponlert, N. Lenghor, S. Kasiwad, L. Srivichai, S. Lapanantnoppakhun, J. Jakmunee, K. Grudpan, Anal. Sci. 20 (2004) 837.
- [19] W.T. Suarez, H.J. Vieira, O. Fatibello-Filho, Ecl. Quim. 30 (2005) 21.
- [20] Z. Bouhsain, S. Garrigues, A. Morales-Rubio, M. de la Guardia, Anal. Chim. Acta 330 (1996) 59.
- [21] A. Criado, S. Cardenas, M. Gallego, M. Valcarcel, Analyst 125 (2000) 1179.
- [22] C. Aniceto, O. Fatibello-Filho, Quim. Nova 25 (2002) 387.
- [23] F. Priego-Capote, M.D.L. de Castro, Anal. Chim. Acta 489 (2003) 223.
- [24] A.F. Lavorante, C.K. Pires, B.F. Reis, J. Pharm. Biomed. Anal. 42 (2006) 423.
- [25] A.R. Medina, M.L.F. de Cordova, A.M. Diaz, Anal. Chim. Acta 394 (1999) 149.
- [26] A. Ruiz-Medina, M.L. Fernandez-de Cordova, M.J. Ayora-Canada, M.I. Pascual-Reguera, A. Molina-Diaz, Anal. Chim. Acta 404 (2000) 131.
- [27] M.J.A. Cañada, M.I.P. Reguera, A.R. Medina, M.L.F. de Cordova, A.M. Diaz, J. Pharm. Biomed. Anal. 22 (2000) 59.
- [28] P. Ortega-Barrales, R. Padilla-Weigand, A. Molina-Diaz, Anal. Sci. 18 (2002) 1241.
- [29] A.G. Alapont, L.L. Zamora, J.M. Calatayud, J. Pharm. Biomed. Anal. 21 (1999) 311.
- [30] D. Easwaramoorthy, Y.C. Yu, H.J. Huang, Anal. Chim. Acta 439 (2001) 95.
- [31] W. Ruengsitagoon, S. Liawruangrath, A. Townshend, Talanta 69 (2006) 976.
- [32] M.L. Ramos, J.F. Tyson, D.J. Curran, Anal. Chim. Acta 364 (1998) 107.
- [33] J.A.M. Pulgarin, L.F.G. Bermejo, Anal. Chim. Acta 333 (1996) 59.
- [34] M.E. Bosch, A.J.R. Sánchez, F.S. Rojas, C.B. Ojeda, J. Pharm. Biomed. Anal. 42 (2006) 291.
- [35] M. Bedner, W.A. Maccrehan, Environ. Sci. Tech. 40 (2006) 516.
- [36] USP, United States Pharmacopeial XXII, Rockville, MD, U.S Pharmacopeial Convention, 1990.
- [37] B.F. Reis, H. Bergamin-Filho, Quim. Nova 16 (1993) 570.
- [38] J.D. Johnson, R. Overby, Anal. Chem. 41 (1969) 1744.
- [39] A. Criado, S. Cardenas, M. Gallego, M. Valcarcel, Talanta 53 (2000) 417.