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Semiautomated solid-phase extraction manifold with a solvent-level sensor

R.M. Orlando *, S. Rath, J.J.R. Rohwedder

Institute of Chemistry, University of Campinas—UNICAMP, PO Box 6154, 13084-971 Campinas, SP, Brazil

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ABSTRACT

A semiautomated solid-phase extraction manifold for multiple extractions is presented. The manifold utilizes commercial solid-phase syringe cartridges and automatically introduces and elutes all the solvents during the extraction, reducing the typical workload and stress of the analyst. The manifold consists of a peristaltic pump with solenoid valves in a flow circuit that contains transmissive photomicrosensors. The photomicrosensors were used to control the solvent dispenser and the solvent level inside the cartridge. As solvent-level sensors, the photomicrosensors determined the exact time the solvent reached the top frit to avoid sorbent drying and accurately perform the solvent exchange. The repeatability of the manifold to introduce a particular volume of solvent into the cartridges was measured, and the precisions were between 0.05 and 2.89% (RSD). To evaluate the manifold, the amount of two fluoroquinolones in a fortified blank milk sample was determined. The results of the intra- and inter-day precision of multiple extractions from the fortified milk samples resulted in precisions better than 9.0% (RSD) and confirmed that the arrangement of the semiautomated manifold could adequately be used in solid-phase extraction with commercial cartridges.

1. Introduction

Solid phase extraction (SPE) is a widespread sample preparation technique used to determine compounds in complex matrices, such as biological and food samples [1–3]. The main advantages of SPE are pre-concentration, recovery and clean-up potential, large number of available sorbent materials and high automation capacity [1–3].

The simplest way to execute SPE is through cartridges on manifolds operated by vacuum pumps. In this configuration, the solvents and samples are sequentially passed through the sorbent, which prevents solvent mixing and drying of the sorbent. Using a manual manifold, the analyst can theoretically extract more than twenty samples simultaneously; however, in practice, this task is very difficult and stressful. One alternative for analyzing a large number of samples is to use an automated SPE system that can perform hundreds of extractions per day. The automated extraction systems use positive or negative pressure to force the solvent and samples through the cartridges [4–6]. The movement of pistols or syringe pumps associated with ultrasonic sensors or CCD cameras controls the liquid levels [7–9]. The major drawbacks of these systems are their expense, risk of cross contamination (carry over) and limitations in relation to the type, format or size of the cartridges used in the system.

Because of these disadvantages, efforts have been made to develop automated and semiautomated homemade solid-phase extraction systems [10–18]. Usually the systems described in the literature do not use commercial open syringe-type solid-phase extraction cartridges; instead, they typically use disks or homemade sorbent columns used in continuous flow extraction systems [10–18].

In this article, we describe the first semiautomated solid-phase extraction system that employs commercial syringe-type solid-phase extraction cartridges and an electronic circuit containing solvent-level sensors based on an inexpensive phototransmissive key.

2. Experimental

2.1. Reagents and solutions

Marbofloxacin (MAR), enrofloxacin (ENR) and sarafloxacin (SAR) were obtained from Riedel de Haën (Seelze, Germany).

Di-sodium hydrogen phosphate dodecahydrate (Merck, Darmstadt, Germany), citric acid monohydrate (Merck, Darmstadt, Germany), tetraethylammonium bromide (Aldrich, Milwaukee, WI, USA) and sodium chloride (Merck, Darmstadt, Germany) were analytical grade.

Methanol, acetonitrile and tetrahydrofuran (HPLC grade) were supplied by Tedia (Fairfield, OH, USA). High purity water was obtained from a Milli-Q system from Millipore (Bedford, MA, USA).

* Corresponding author. Tel.: +55 19 3521 8782.
E-mail address: orlandoricardo@hotmail.com (R.M. Orlando).

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The fluoroquinolones stock solutions (1 mg mL^{-1}) were prepared by dissolving the standards in 500 μL of glacial acetic acid and diluted to 25 mL with methanol in a volumetric flask.

The working solutions of fluoroquinolones (40.0, 2.0 and 1.0 μg mL^{-1}) were prepared daily by dilution of the stock solution with methanol.

During the SPE procedure, two buffer solutions composed of citric acid and phosphate (CPB) were used. The CPB solutions were prepared by mixing appropriate quantities of citric acid and disodium hydrogen phosphate solutions to obtain final solutions with a pH of 4.0. The concentrations of the citric acid and disodium hydrogen phosphate solutions are described below:

(1) 10 mmol L^{-1} citric acid and 20 mmol L^{-1} disodium hydrogen phosphate is herein referred to as CPB 10/20.
(2) 100 mmol L^{-1} citric acid and 200 mmol L^{-1} disodium hydrogen phosphate is herein referred to as CPB 100/200.

2.2. SPE cartridge and flow extraction system

The SPE cartridges were all homemade. The empty polypropylene SPE cartridges (6-mL capacity) and the polytetrafluoroethylene (PTFE) frits were obtained from Varian (Palo Alto, CA, USA). The sorbent was composed of 500 mg of Sepra-C18-E (50-μm particle size and 65-Å pore size) from Phenomenex (Torrance, CA, USA).

PTFE or silicon tubing (i.d. = 1.5 mm for both) formed the connection between the valves and the solvent bottle. Stainless steel syringe needles were used to connect the SPE cartridge to the PTFE tubing (2.0 × 100 × 1.6 mm ∅, Höppner, São Paulo, SP, Brazil).

The solenoid valves and optos were controlled by a parallel interface, PCL 9111 ADLink Technology (Taipei, Taiwan), connected to a computer and an electronic circuit specifically constructed for the manifold. The electronic circuit was presented in previous articles that described the use of solenoid valves and optos [19]. The flow rate was maintained by a peristaltic pump (Ismatec IPC, Switzerland) model 78001-22 and 3.2 mm (i.d.) Viton® tubing (Ismatec IPC, Switzerland). The peristaltic pump was connected to the computer by the RS-232 parallel interface.

The semiautomated solid-phase extraction manifold was controlled by an AMD Sempron (AMD, USA) compatible microcomputer (902 MHz, 992 Mb of RAM) that ran controlling software written in Visual Basic 6.0 (Microsoft, Redmond, WA, USA).

The principal electronic components used in the flow extraction system were fourteen solenoid three-way valves (24 V) from N Research (West Caldwell, NJ, USA), four PHCT203 transmissive photomicrosensors (opto) from Politronic (São Paulo, SP, Brazil) and three EE-SX461-P11 transmissive photomicrosensors (opto) from Omron. A diagram of the flow extraction system is shown in Fig. 1.

The solvent dispenser was responsible for generating and introducing aliquots of solvents with fixed volumes into the cartridges during the conditioning, washing and eluting steps (dashed lines in Fig. 1).

The solvent sensors P_L were composed of the optos working in tandem with the valves, S_W and S_C (dotted line, Fig. 1). These sensors were responsible for eluting the conditioning and washing solvents, the sample and the analyte-containing solvent (extracted from milk). The analyst manually introduced the sample after the sorbent was automatically conditioned. After the sample was inserted into the cartridge with a pipette, the level sensor automatically restarted the sample elution, washing and final elution steps.

The photosensitive region of the level optos is positioned immediately above the top PTFE frits (Fig. 2A and B). When liquid is in the optical path length, the light from the phototransmissive diode does not reach the photoreceptive diode (Fig. 2A). During this time, a signal is sent from the interface to open or close the solenoid valves. However, when liquids run through the photosensitive region of the level optos, the light from the phototransmissive diode reaches the photoreceptive diode and changes the status of the signal (Fig. 2B). In this arrangement, the level optos responds to the liquid–air or air–liquid transition on top of the PTFE frit.

A support was needed to assemble the level optos (Fig. 3A). The support was constructed of acrylic and used to center the cartridge between the photo diodes and to keep the wall of the cartridge 5.5 mm away from the case of the opto (Fig. 3A and B). This approach was used to place an adequate portion of the cartridge (reservoir) inside the optical path length (Fig. 3B). In this position, the sensitivity of the level opto could be adjusted appropriately to recognize changes to the signal when air or liquid were positioned between the photodiodes, independent of the composition of the liquids (organic, aqueous, organic–aqueous or sample).

Described below is an example of a solid-phase extraction sequence followed by employment of the semiautomated manifold with one cartridge and one solvent (one bottle) during the conditioning, washing and final elution steps.

Stage 1—Pre initialization: The extraction was initialized with the flow circuit completely empty from the common point C_1 to the cartridges. Before solvent one was introduced into the cartridges, it was recirculated in B_1 by keeping PP on and the S_{S1} valve closed.
Stage 2—Generation of aliquots of solvent: To generate aliquots of solvent one, the S_{S1} and S_{I1} valves were opened. The solvent filled the PTFE loop tubing (i.d. = 1.6 mm) until the front of the solvent reached opto P_V and generated a 1.55-mL aliquot of solvent. When the aliquot reached opto P_V, the solvent changed the signal of the opto, which closed the S_{S1} valve and opened the S_{Air} valve. The S_{Air} valve remained opened for a fixed period of time (10 s). If the analyst chooses more than one aliquot of solvent, the S_{Air} valve closes and the S_{S1} valve opens to introduce another aliquot of the same solvent. Otherwise, the S_{Air} valve remains opened to carry the unique aliquot of solvent into the target SPE cartridge.
Stage 3—Introduction of aliquots of solvent into the cartridge (conditioning, washing and final elution steps): When the aliquots of solvent are introduced, the S_{Air} and S_{I1} valves remained open. A transition liquid–air in the signal of opto P_{I1} determined when the solvent was introduced into the cartridge. After the solvent was completely introduced, the opto P_{I1} changed its signal status and closed the S_{Air} and S_{I1} valves.
Stage 4—Elution (conditioning): After complete introduction of the solvent, the opto P_{L1} started to detect the liquid in the cartridge. While the opto P_{L1} was detecting the liquid, a signal was sent to keep the S_{W1} valve opened. Meanwhile, the liquid was removed by the PP and sent to W_B. When elution was complete, the transition from liquid to air was detected by opto P_{L1}, and the S_{W1} valve was closed.
Stage 5—Sample introduction: Subsequent to conditioning, the samples were introduced manually by the analyst with a pipette. As soon as the samples were introduced, the signal of opto P_{L1} changed (air–liquid transition), and sample elution was automatically restarted by the system, as described in Stage 4.
Stage 5—Washing: This step was carried out automatically by repeating Stages 2–4 for the predefined solvent.
Stage 6—Introduction of the final elution solvent: The final elution solvent was introduced automatically into the cartridge by repeating Stages 2 and 3.
Stage 7—Elution and collection of the analytes: After the final elution solvent was completely introduced, the opto P_{L1} started

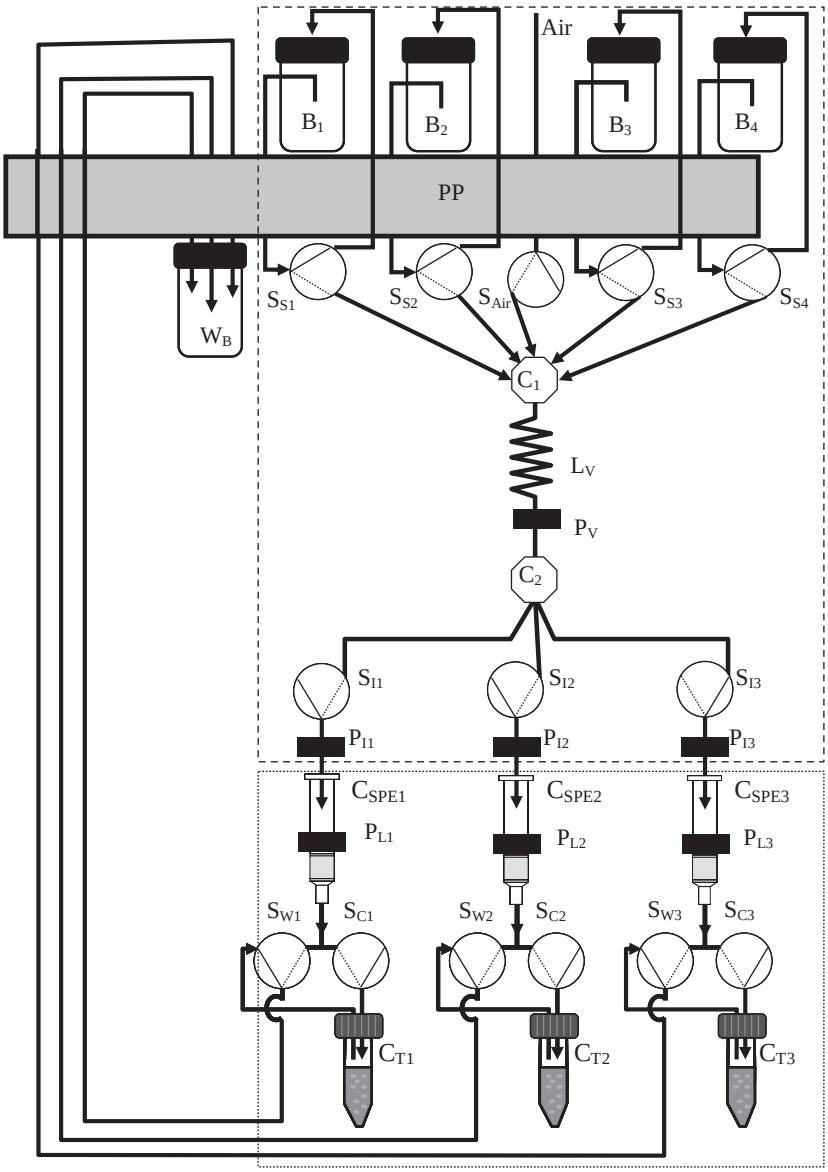

Fig. 1. Diagram of the flow extraction system developed for SPE. The dashed square contains the solvent dispenser of the system. The dotted square contains the solvent-level sensor and the system's eluting valves. C_T=collector tubes, C_{SPE}=solid-phase extraction cartridges, C=common point, L_V=volumetric loop, P_I=solvent introduction controller phototransmissive key, P_L=level controller phototransmissive key, P_V=volume controller phototransmissive key, PP=peristaltic pump, B=solvent bottles, S_I=solvent solenoid valves entrance, S_{Air}=air line solenoid valve, S_C=collector tube solenoid valves, S_S=solvent line solenoid valves, S_W=waste line solenoid valves and W_B=waste bottle.

to detect the liquid in the cartridge. While the opto P_{L1} was detecting liquid, the signal was sent to keep valves S_{W1} and S_{C1} open. Meanwhile, the PP removed the solvent containing the analytes from the cartridge and sent it to collector tube C_{T1}. Even after the opto P_{L1} detected the transition from liquid to air, the S_{W1} and S_{C1} valves remained open for an additional 4 min to remove all the residual solvent from the cartridge and the flow circuit of the manifold to the collector tube C_{T1}.

The liquid residues from the conditioning step, sample introduction and washing steps were sent to the waste bottle W_B.

The volume of solvent, number of solvents and cartridges used, as well as the flow rate employed for each solid-phase extraction step, were determined by the analyst using the program written in Visual Basic language.

When the analyst selected more than one cartridge and solvent for each step, the manifold began introducing the first solvent into all of the cartridges followed by simultaneous elution. In sequence, the system restarted and introduced the second solvent followed by the other solvents if required.

2.3. Measurement of the volume of solvents introduced into the cartridge by the manifold

To evaluate the precision of the solvent dispenser of the manifold, aliquots corresponding to two times the volume of the loop were weighed on a calibrated analytical balance (accuracy of ± 0.1 mg). Four measurements ($n=4$) for each solvent were collected manually in a collector tube at the typical position of each cartridge. The solvents were collected at the same time during the extraction sequence as employed for the extraction of the milk samples. The volume was calculated based on the density of each solvent and determined with a calibrated 50-mL volumetric flask.

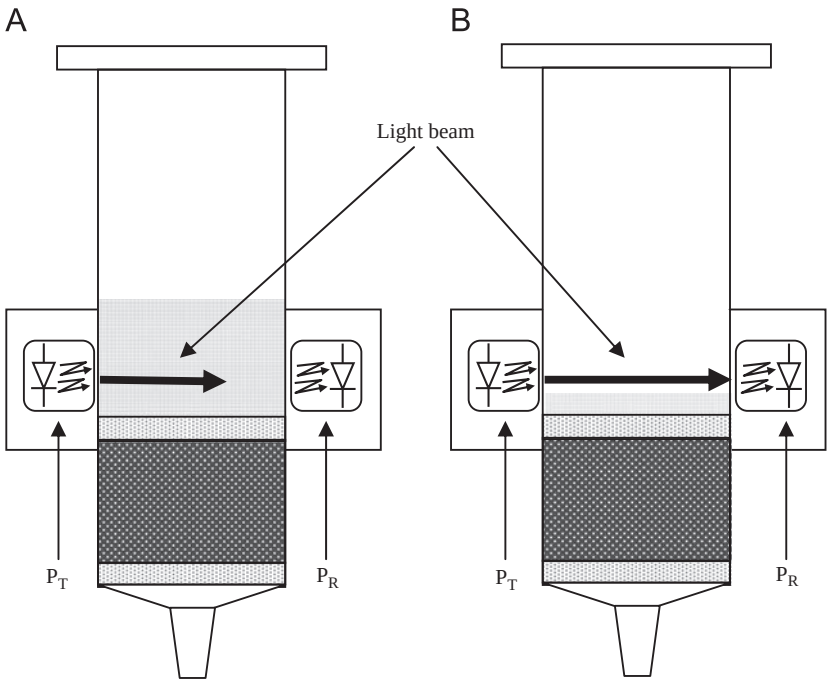

Fig. 2. Representation of the level opto operation. (A) Front view depicting when the liquid level inside the cartridge absorbs the light from the phototransmissive diode preventing it from reaching the photoreceptive diode. (B) Front view depicting when the liquid level inside the cartridge is low enough to allow the beam of light from the phototransmissive diode to reach the photoreceptive diode. P_T=phototransmissive diode and P_R=photoreceptive diode.

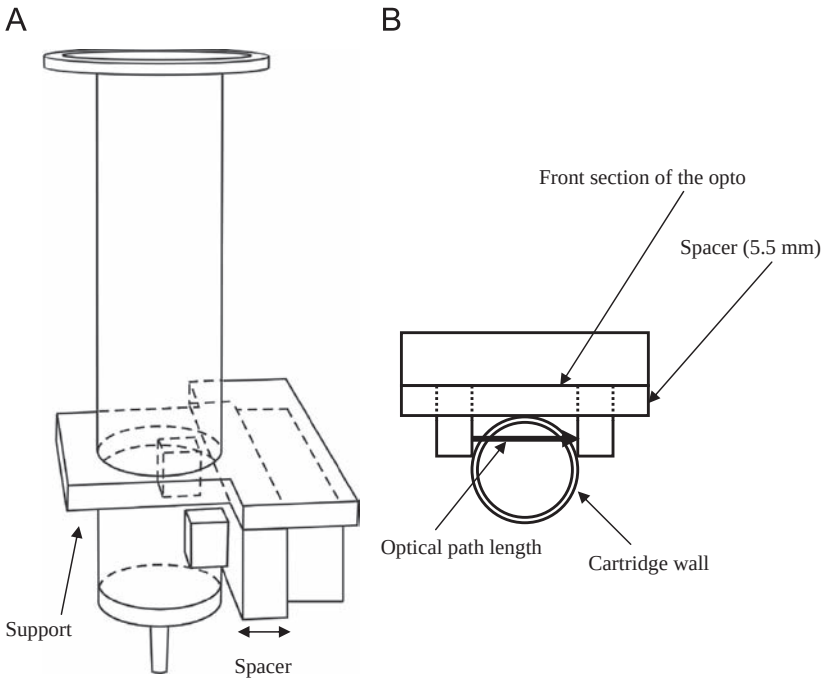

Fig. 3. Representation of the level opto positioned around the SPE cartridge. (A) Lateral view and (B) upper view of the opto; the support and the spacer were made of acrylic and used to position the cartridge 5.5 mm away from the front section of the opto.

2.4. Calibration curves of fortified milk samples

MAR and ENR were determined in fortified blank milk samples after extraction by SPE. The blank milk samples were fortified with working solutions of MAR and ENR, as described in Section 2.5.

Blank milk samples were fortified with MAR and ENR at five concentrations: 18.7, 37.5, 75.0, 112.5 and 150.0 ng mL^{-1} MAR and 25.0, 50.0, 100.0, 150.0 and 200.0 ng mL^{-1} ENR. The calibration curves were carried out in triplicate at each concentration level (n=3).

First, the proteins in the milk sample (volume of 1 mL) were precipitated by adding 0.4 mL of trichloroacetic acid (30%, w/v) in methanol. The sample was agitated for 30 s on a vortex mixer and centrifuged for 15 min at 4186 *g*. The supernatant was collected (first supernatant), and the residue was washed with 1 mL of CPB 100/200. The residue and washing solution were re-agitated on the vortex mixer for 30 s and centrifuged again for 15 min at 4186 *g*. The second supernatant was combined with the first, added to 3 mL of CPB 100/200, homogenized and subjected to solid-phase extraction. For SPE, the cartridge was conditioned with 3.1 mL of

1.5% (v/v) acetic acid in methanol, followed by 3.1 mL of water and 3.1 mL of CPB 100/200 at pH 4.0. The supernatants obtained from the protein precipitation of the sample were then loaded onto the cartridge. Then, 3.1 mL of CPB 10/20 containing 5% (v/v) of tetrahydrofuran was used for the washing step. Finally, the analytes were eluted with 3.1 mL of 1.5% (v/v) acetic acid in methanol. The flow rate used during extraction was 3.0 mL min^{-1} for the conditioning, sample introduction and washing steps. During the final elution, the flow rate was maintained at 0.5 mL min^{-1}.

The eluent was concentrated to dryness at 45 °C under a flow of nitrogen. The residue was dissolved in 500 μL of mobile phase (1:1, A/B, v/v) containing 100 ng mL^{-1} of SAR (internal standard). Before HPLC-FLD analysis, the solutions were filtered through a 0.22-μm membrane filter.

2.5. Determination of fluoroquinolones in fortified blank milk samples

Blank milk samples were fortified with MAR and ENR at three concentrations: 37.5, 75.0 and 112.5 for MAR and 50.0, 100.0 and 150.0 ng mL^{-1} for ENR. The samples were analyzed on three different days. On the first day, each concentration level was analyzed five times ($n=5$). On the second and third days, the samples were analyzed in triplicate ($n=3$) for each concentration level. The extractions were carried out using the same method described for the calibration curve (Section 2.4).

2.6. Quantitation of fluoroquinolones using high performance liquid chromatography

The fluoroquinolones were analyzed on a 1200 HPLC system (G1322A degasser, G1311A quaternary gradient pump, G1329A auto sampler, G1316A column thermostat, G1321A fluorescence detector and ChemStation data acquisition software) purchased from Agilent (Palo Alto, CA, USA).

The fluoroquinolones were separated on a Purospher™Star column (100 × 4.0 mm, 3.0 μm) (Merck, Darmstadt, Germany). The mobile phase was composed of (A) 50 mmol L^{-1} sodium phosphate at pH 2.6, containing 0.05% (w/v) tetraethylammonium bromide and (B) methanol:acetonitrile (1:1, v/v). Gradient elution was used to separate the fluoroquinolones: 88:12 (A/B, v/v) for 17.5 min, changed to 73.8:26.2 (A/B, v/v) (17.5–17.6 min), maintained at 73.8:26.2 (A/B, v/v) for 3.4 min, returned to 82:18 (A/B, v/v) at 21.1 min and maintained at 82:18 (A/B, v/v) at 26 min. The flow rate and temperature were 1.1 mL min^{-1} and 45 °C, respectively. The injection volume was 10 μL. Quantitation was performed by internal calibration using the following wavelengths on the fluorescence detector: 290 nm (excitation) and 530 nm (emission) for MAR and 290 (excitation) and 480 (emission) for ENR and SAR (internal standard).

3. Results and discussion

First, the semiautomated solid-phase extraction system was evaluated to certify that the solvent dispenser was able to accurately introduce the same volume of solvent into the SPE cartridges. The total volume of each solvent (3.1 mL) was introduced as two 1.55-mL aliquots, as determined by the fixed loop and the response of the opto (L_V and P_V, Fig. 1) to the transition from air to liquid. Four different solvents were introduced into the cartridges during each SPE step. In this manifold configuration, the solvent aliquots may be altered by the differing physicochemical properties of the solvents, changes in the reaction time of the opto and the different pathways followed by the solvents in the flow circuit. Depending on the wettability of the solvent, it may form a residual film on the tubing that can interfere with the response of the opto. However, when the sensitivities of the optos are adjusted correctly, their response to different solvents must be similar, especially during the washing and final eluting steps, where variations in the solvent volume can vary the recovery of the analytes. The results of measuring the solvent volumes introduced into the cartridge by the solvent dispenser are shown in Table 1.

The similarities among the results for the four different solvents presented in Table 1 demonstrated that the solvent dispenser composed of the fixed loop and the opto was able to introduce aliquots of solvent with adequate precision for SPE. For the four solvents tested, the mean values were approximately 3.1 mL regardless of the composition of solvent: organic only (solvent 1), pure aqueous (solvents 2 and 3) or organic–aqueous mixture (solvent 4). The results also indicate that the sensibility of the opto was correctly adjusted, which resulted in equivalent response times for each trial. In the presented manifold, only the loop volume and the opto response determined the volume of solvent. Therefore, any variation in the flow rate, originating from the peristaltic pump, would not significantly alter the volume of solvent introduced into the cartridges.

In manual solid-phase extraction manifolds, there are two critical points during the extraction. The first critical point occurs during liquid elution to avoid sorbent drying. Multichannels in the sorbent are formed if it dries, and the efficiency of extraction decreases. The other critical point is associated to the moment when one solvent is replaced by the subsequent one. If the exchange is made too early, the solvents mix and reproducibility is compromised. It is extremely hard for the analyst to avoid these two problems; therefore, in the presented manifold, we utilized a solvent-level sensor to control these critical points. This sensor was composed of an opto similar to that used to generate the solvent aliquots. Therefore, it was important to determine if the solvent-level sensor was able to appropriately change its status as the level of liquid in the cartridge changed, as described in Fig. 2A and B. Ideally, the flow must be stopped or the solvent or sample must be introduced into the cartridges if the level of the predecessor liquid reached the top of the top PTFE frit. If the status of the sensor level changes too early, the exchange among liquids will be impaired, and the recovery or clean-up may be reduced.

Table 1
Mean values and relative standard deviations (RSD) ($n=4$) of the solvent volumes introduced into the SPE cartridge by the semiautomated extraction system.

	Solvent 1		Solvent 2		Solvent 3		Solvent 4		Solvent 5	
	Mean (mL)	RSD%	Mean (mL)	RSD%	Mean (mL)	RSD%	Mean (mL)	RSD%	Mean (mL)	RSD%
Cartridge 1	3.05	0.28	3.12	2.89	3.14	0.92	3.10	0.24	3.11	0.82
Cartridge 2	3.16	0.32	3.12	0.38	3.12	0.05	3.11	0.47	3.14	0.66
Cartridge 3	3.08	0.26	3.10	0.36	3.13	0.15	3.12	1.02	3.08	0.72

Solvent 1 = 1.5% (v/v) acetic acid in methanol; solvent 2 = deionized water; solvent 3 = CPB 100/200 at pH 4.0; solvent 4 = CPB 10/20 at pH 4.0 with 5% (v/v) of tetrahydrofuran; solvent 5 = same solvent used for solvent 1 but introduced into the cartridge during the final elution step.

Table 2
Mean values and relative standard deviations (RSD) of intra- and inter-day precision for the determination of two fluoroquinolones in fortified blank milk samples.

Intra-day (5 samples per concentration)					
Theoretical concentration (ng mL^{-1})	MAR		Theoretical concentration (ng mL^{-1})	ENR	
	Mean (ng mL^{-1})	RSD %		Mean (ng mL^{-1})	RSD %
37.5	39.8	7.3	50.0	54.0	5.7
75.0	78.8	3.1	100.0	104.0	3.4
150.0	154.0	2.2	200.0	202.7	2.3
Inter-days (3 days; total of 11 samples per concentration)					
Theoretical concentration (ng mL^{-1})	MAR		Theoretical concentration (ng mL^{-1})	ENR	
	Mean (ng mL^{-1})	RSD %		Mean (ng mL^{-1})	RSD %
37.5	37.5	8.9	50.0	52.0	6.4
75.0	78.0	2.3	100.0	104.0	2.7
150.0	153.0	2.8	200.0	201.3	6.9

However, if the sensor level changes too late, the sorbent will dry out.

To verify if the semiautomated system worked appropriately with a real sample, milk samples were fortified with two fluoroquinolones and submitted to SPE after protein precipitation using the flow extraction system. This procedure was repeated for three days, and the results (intra and inter day) are shown in Table 2.

The intra- and inter-day precision results for the three fortification levels (ng mL^{-1}) demonstrated that the SPE steps were performed properly. The precision obtained with the semiautomated manifold was comparable to those obtained using a manual manifold, which requires time and effort from the analyst to correctly introduce the solvents and the samples and to simultaneously control the flow rate of the cartridges. It is important to emphasize that the precision results shown in Table 2 did not represent the actual RSD of the semiautomated system because there are other contributions to the uncertainty of the analytical method, such as protein precipitation and chromatography analysis. Based on the precision of the solvent introduction step, shown in Table 1, a lower RSD is expected for the semiautomated system if the SPE procedure could be evaluated separately.

Another important advantage of our semiautomated system is that the solid-phase extraction step carried out by the analyst is the introduction of the sample, which could be performed any time once the PC indicates that the conditioning step is complete. We chose to have the analyst introduce the sample into the cartridge to avoid cross contamination of the flow circuit, which sometimes occurs with commercial automated solid-phase extraction systems.

4. Conclusions

The results for the quantitation of fluoroquinolones in milk demonstrated that the sensors worked adequately, and the semiautomated manifold was able to precisely extract the samples. The automated manifold substantially reduced the stress and effort required from the analyst and demands only that the samples be introduced manually into the cartridge. The manifold is highly flexible because it uses commercially available cartridges. The solvent dispenser composed of a fixed loop, solenoid valves and photomicrosensor was able to introduce volumes of solvent with adequate precision. The photomicrosensor employed as a solvent-level sensor was able to accurately detect the liquid–air and air–liquid transitions at the cartridge's top frit, which avoided drying of the sorbent and allowed for correct solvent exchange. In this study, the innovative sensor level was used with peristaltic pumps and solenoid valves; however, this device is highly flexible and inexpensive and could be utilized with other automated and semiautomated solid-phase extraction instruments or manual manifolds.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.talanta.2013.04.077.

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