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Development of a multicommuted flow-through optosensor for the determination of a ternary pharmaceutical mixture

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Abstract

The combination of multicommutation and flow-through multioptosensing is presented in this work as a powerful strategy for the routine analysis of active principles in pharmaceuticals. By coupling methodologies, the selectivity and sensitivity of optosensors is maintained, while the use of the multicommutation approach provides additional advantages, such as low reagent consumption, low waste generation and reduced human supervision. The potential of this integration is enhanced when implemented with multiwavelength detection mode. An UV sensor is here developed for the simultaneous determination of three widely used active principles: salicylamide, caffeine and propyphenazone. The measuring wavelengths were 276 nm for caffeine and propyphenazone, and 302 nm for salicylamide. The five three-way solenoid valves used in the system are controlled by Java-written home-made software. The sensor is based on the on-line selective retention of two of the three analytes on a precolumn placed just before the sensing zone and filled with the same solid support than the flow-through cell (C_{18} silica gel). This approach allows the sequential arrival of the analytes to the sensing zone, so allowing their determination with only one sample injection. So, the use of C_{18} placed, in both the precolumn and the flow-cell combines the advantages of the increase of sensitivity and selectivity in the detection solid zone with the additional increase of the selectivity in the precolumn. The sensor was applied to the determination of the analytes in several pharmaceutical preparation of the Spanish Pharmacopoeia, obtaining satisfactory results.

Keywords: Multicommutation; Flow-through optosensor; Pharmaceuticals

1. Introduction

The development of automated methodologies for the routine analysis of pharmaceuticals is increasing each year. This is due to the high demand of rapid and low-costly simultaneous analysis of several active principles. Not only are these characteristics improved with the use of automation, but also better repeatability of the determinations, reduced reagent consumption and low waste generation are achieved [1]. In conclusion, automation means not only improvement in economy and analytical results, but also the development of environmentally friendly methods.

Multicommutation refers to the use of solenoid valves, automatically controlled by home-made software, which can be individually switched on and off and allows a very simple manipulation of the flow network [2,3]. By only disconnecting one valve and placing it in a different way the whole system can be reused for a completely unlike application. The possibility of different applications by using the same manifold is also available by only altering the order in which the valves are switched on and off.

The potentiality of flow-through optosensing has been previously demonstrated both with UV photometric [4–6] or fluorimetric [7–9] detection. The main advantages of this methodology are a great sensitivity (comparing to typical analysis in solution due to the preconcentration of the analytes in the detection zone) and selectivity. The later is obtained by means of selective retention of the target analytes on the solid support used, while the possible interfering compounds pass through the sensing zone interstices, so the analytes can develop their signals without analytical errors occurring. The selectivity has been previously enhanced in some works by means of a precolumn filled with solid support placed before the flow-through cell [10]. This approach has permitted the selective retention of one or more target analytes on the solid micro-beads in the precol-

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umn while another one developed its signal in the sensing zone; after that, the next target analyte was eluted from the support and carried towards the sensing zone developing its signal.

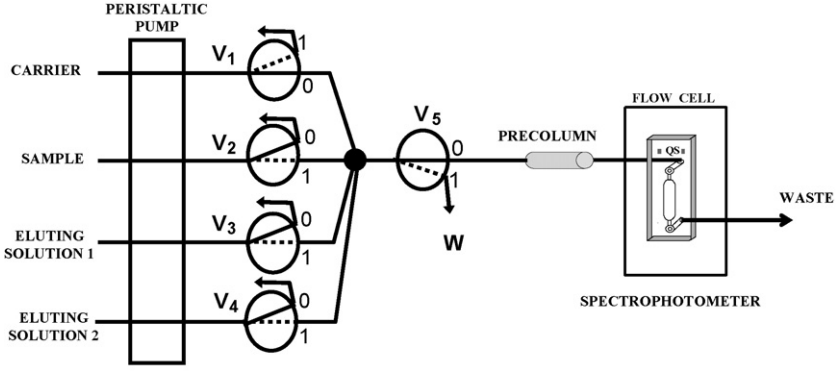
Although the coupling of multicommutation and optosensing has been previously reported [11,12], this is the first triparameter optosensor developed up to date using this coupled methodology. Comparing classical flow injection analysis (FIA) and the proposed work, the sample and reagents saving was 40–90%. This is due to the fact that in classical FIA all the solutions are continuously consuming, while in multicommutation the solutions are recycling to their respective vessels and not circulating through the system, unless otherwise specified by the software; so multicommutation helps to develop environmentally friendly routine methods of analysis. An additional advantage of multicommuted systems when comparing to classical FIA designs is the economy; solenoid valves are much cheaper than six port valves (usually used in FIA flow networks). Finally, a complete automation can be achieved by using multicommutation.

In this multicommuted optosensor, the strategy of a precolumn filled with the same solid support that the flow-through cell, silica gel C_{18}, has been used. As model analytes we have chosen three active principles: salicylamide (SLC), caffeine (CF) and propyphenazone PZC), which show different selective retention on the solid support: Two of the analytes, CF and PFZ, were retained on the solid support in the precolumn; SLC passed through it and reached the sensing zone, where it developed its transitory signal. After that, by means of two different methanol/water solutions, CF (25%, v/v) and PFZ (60%, v/v) were selectively and successively eluted and carried towards the sensing area, developing their analytical signals. In this way, the on-line separation of the analytes in the precolumn before the UV solid phase detection, combines the advantages of sensitivity and selectivity of the absorbance measurements of the analytes on the sensing zone with the additional increase in the selectivity by means of the different kinetics of retention/elution of the analytes in the precolumn. The analytical signal was the intrinsic UV absorbance, measured at 276 nm for CF and PFZ, and 302 nm for SLC. The developed strategy allowed the determination of the three analytes by a single sample injection in the flow network, so simplifying the manifold. Furthermore, minor sample treatment is required and no prior extraction is need. The sensor has been applied to the determination of the analytes in several pharmaceuticals preparations of the Spanish Pharmacopoeia, obtaining satisfactory results. In addition, a recovery study was carried out in order to check the accuracy of the system, as it turned out.

2. Experimental

2.1. Reagents and materials

Caffeine (Fluka, Buchs, Switzerland) stock standard solution of 800 mg L^{-1} was prepared in deionized water. Salicylamide (Fluka) and propyphenazone (Guinama, Valencia, Spain)



Step	V_1	V_2	V_3	V_4	V_5	Time (s)	Description
1º	0	0	0	0	0	100	C_{18} conditioning
2º	1	1	0	0	0	50	Sample introduction
3º	0	0	0	0	0	170	SLC signal
4º	1	0	1	0	0	90	CF signal
5º	1	0	0	1	0	90	PFZ signal
6º	1	1	0	0	1	10	Cleaning step 1
7º	0	0	0	0	1	25	Cleaning step 2

Fig. 1. Design of the flow network. V: valve; eluting solution 1: 25% MeOH; eluting solution 2: 60% MeOH. Scheme of the valves switching procedure: 0 means off and 1 means on.

stock solutions of 800 mg L^{-1} were prepared by dissolving the required weight in the minimum volume of methanol and diluting to 100 mL with deionized water. Solutions were kept in the refrigerator protected from light.

Potassium di-hydrogen phosphate, di-potassium hydrogen phosphate, ammonium chloride, ammonia and methanol were purchased from Panreac (Barcelona, Spain). All needed solutions were prepared in deionized water.

C_{18} bonded phase silica gel beads (Waters, Milford, USA) with 55–105 μm of average particle size were used as sensing support. Sephadex QAE A-25 (40–120 μm) from Sigma–Aldrich was also tested.

2.2. Instrumentation and flow network

The flow network is depicted in Fig. 1. It was built using a four-channel Gilson Minipuls-3 (Villiers Le Bell, France) peristaltic pump with rate selector and pump tubing type Solvflex (Elkay Products, Shrewsbury, MA, USA). An electronic interface based on ULN 2803 integrate circuits was employed to generate the electric potential (12 V) and current (100 mA) required to control the five 161T031 NResearch three-way solenoid valves (Neptune Research, MA, USA). The software for controlling the system was developed in Java. PTFE tubing of 0.8 mm i.d. and methacrylate connections were also used.

All spectral measurements and real-time data acquisition of flow signals were made with a Varian Cary 50 (Madrid, Spain) spectrophotometer controlled by means of a PC fitted with the Varian computerized spectroscopy software, WIN-UV.

Measurements were continuously recorded at the maximum absorbance wavelengths of the analytes, which were 276 nm for CF and PFZ and 302 nm for SLC (measuring at several wavelengths is an additional possibility of the software controlling the instrument). A Hellma 138-QS flow cell (1 mm light path, 50 μL inner volume) was used to accommodate the silica gel C_{18} micro-beads. A precolumn (40 mm length, 1.5 mm i.d.) packed with 40 mg of C_{18} solid support was placed in the manifold just before the flow cell, in order to obtain the optimal separation of the analytes. Some glass wool was used in the outlet of cell and precolumn to avoid loosing solid support.

2.3. Sample preparation

The pharmaceutical samples were chosen in several presentation ways. The samples were powdered and homogenized (if necessary) and dissolved with 5% MeOH, filtered and diluted to volume with deionized water in a volumetric flask. Sonication was used in all cases in order to facilitate dilution.

Suitable dilutions with phosphate buffer (0.2 M, pH 7) were made before measuring.

2.4. General procedure

The flow diagram of the system and the valves switching scheme are depicted in Fig. 1. In the initial status, all valves are switched off (0) and the carrier, ammonia/ammonium chloride 0.2 M at pH 8.6, is flowing through the flow cell while all other solutions are recycling to their vessels. The sample is introduced by simultaneously switching the valves V_1 and V_2 on (1) for 50 s. CF and PFZ are strongly retained on the C_{18} micro-beads placed in the precolumn and SLC, which passes through it and reaches the sensing zone, develops its transient analytical signal and is eluted by the carrier itself. After SLC has developed its signal (λ = 302 nm), by switching valves V_1 and V_3 on, the 25% MeOH eluting solution is introduced in the flowing system for 90 s; so CF is eluted from the precolumn and carried towards the cell, where it now develops its transitory signal (λ = 276 nm). Finally, PFZ is eluted by means of a 60% MeOH solution (turning valves V_1 and V_4 on during 90 s) and is detected in the sensing zone (λ = 276 nm). In order to avoid any possible contamination between samples, the portion of tubing placed between valves V_1 and V_5 was cleaned. This is achieved by opening valves V_1 and V_2 for 10 s and V_5 for 25 s.

The sample solution is prepared in phosphate buffer 0.2 M at pH 7. Calibration standards and samples were analyzed by triplicate. A profile of the transient signal showing the separation of the three analytes is shown in Fig. 2.

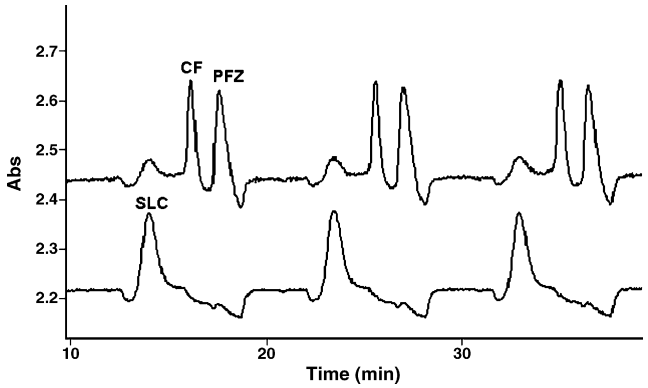


Fig. 2. Profile of the transient signal of 8, 4 and 5 μg mL^{-1} SLC, CF and PFZ, respectively, by triplicate.

3. Results and discussion

3.1. Spectral characteristics

The spectral features of the analytes were recorded both in aqueous solution and solid-phase media. The analyte spectra were overlapped, so making impossible the simultaneous determination without significant analytical errors. The spectra of the analytes are depicted in Fig. 3.

The strategy of the precolumn (filled with solid support) placed just before the detection area makes it possible the sequential arrival of the analytes to the solid phase detection zone, where their individual analytical signals can be monitored separately. The use of multiwavelength detection provides an additional advantage, that is, the monitoring of the analytes at their maximum wavelength, so improving the obtained sensitivity. The chosen wavelengths were 276 nm for CF and PFZ and 302 nm for SLC.

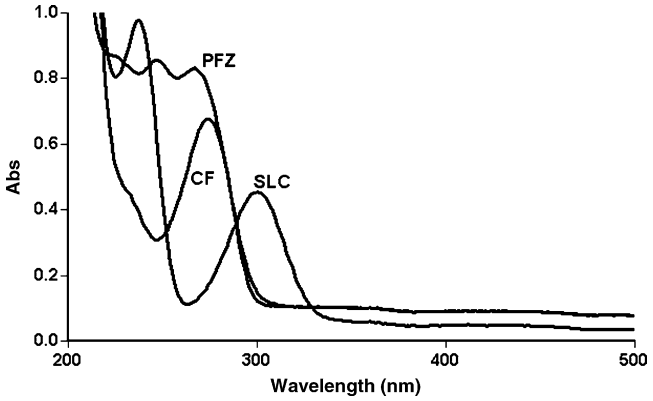


Fig. 3. Absorbance spectra of 10 μg mL^{-1} CF and PFZ, and 15 μg mL^{-1} SLC.

3.2. Selection of the solid support in the cell and in the precolumn

Two solid supports were tested in the flow network: an anionic resin, Sephadex QAE-A25, and a non-ionic solid support, silica gel C_{18}. Although SLC was retained on the Sephadex solid support (it has a pK_a value of 8.4), CF and PFZ were not retained due to their non-ionic nature; therefore this solid support was ruled out. C_{18} silica gel was able to retain all the analytes and, depending on the nature of the carrier and eluting solutions used, could interact with the target compounds providing the required selectivity. Therefore, C_{18} silica gel was used both in the flow-through cell and in the precolumn. The different kinetics of retention/elution of the compounds made possible the adsorption of CF and PFZ on the solid support in the precolumn, while SLC developed its signal on the sensing zone (when using the suitable pH). Then both retained analytes could be selectively desorbed, being sequentially detected in the flow cell. The precolumn used had a 1.5 mm i.d. and 40 mm length of solid phase (40 mg) was enough for a proper separation of the analytes. Higher amounts of solid support decreased the signal, as the dispersion of the analytes in the solid beads increased.

3.3. Chemical variables

3.3.1. Selection of the carrier solution

The study of the pH of the carrier was carried out taking into account the nature of the analytes. SLC remains in an anionic form for basic pH, CF and PFZ remain in a non-ionic nature in the pH range 2–14. Due to the pK_a value of SLC, a slight signal decrease was observed when increasing the pH value above 7, due to the lower retention on the C_{18} solid beads because of its acquired charge; consequently, the elution time also decreased. CF and PFZ were strongly retained independently of the pH value used. A pH value of 8.6 was selected as optimum and the best results were obtained by using an ammonia/ammonium chloride buffer. The buffer concentration was studied ranging from 0.04 to 0.4 M. As the concentration increased, the elution time decreased but non-significant decrease in the signal was observed up to 0.2 M, so choosing this last one as optimum value.

3.3.2. Sample solution

The signal of SLC increased when increasing the pH value up to 7, diminishing for higher pH, while CF and PFZ signals remained constant. Therefore, 7 was the selected value. The elution time did not significantly vary in the pH studied range, which was 5–10; so this variable had not to be taken into account. A phosphate buffer provided good results, and its concentration was tested from 0.02 to 0.4 M. Both the obtained signals and elution time remained constant; so 0.2 M was selected in order to provide enough buffer capacity.

3.3.3. Eluting solutions

After the carrier itself eluted SLC from the solid sensing zone, CF and PFZ had to be selectively eluted from the solid support in the precolumn. The usual working mode to clean silica gel C_{18} is by using alcoholic solutions; therefore different percentages of MeOH:water solutions were tested: 15–35% for CF and 30–70% for PFZ, which was strongly retained.

In the case of CF, the signal increased up to 25%, diminishing for higher percentages. For PFZ a constant increase in signal was observed up to 70%, but methanol content above 60% made the signal less reproducible. For both analytes, increasing MeOH percentage meant improving sample frequency. Finally, 25% and 60% MeOH:water were chosen, in order to obtain the best possible signal with satisfactory repeatability and sample throughput.

3.4. Flow system variables

The sample introduction time and the flow-rate provided by the peristaltic pump were the studied flow system variables. In the case of multicommuted flow networks, the sample volume is controlled by changing the insertion time, and not by using different sample insertion loops (as classical FIA). The studied range was from 10 up to 100 s. When increasing insertion sampling time for the same sample concentration, the signal increased due to higher amounts of analytes being introduced into the flow system and, hence, reaching the sensing zone. The signal increased linearly up to 60–80 s, depending on the analyte. It is important to notice that although the sensitivity increased when using high insertion times, the sample frequency diminished, so a compromise between both variables had to be taken into account. Finally 50 s was chosen, as a high sample fre-

Table 1
Analytical parameters

Parameter	SLC	CF	PFZ
Linear dynamic range (μg mL^{-1})	2–40	0.7–15	1–20
Calibration graph			
Intercept	0.0068	−0.036	0.0051
Slope (mL μg^{-1})	0.0207	0.0639	0.055
Correlation coefficient	0.9999	0.9996	0.9984
Detection limit (μg mL^{-1})	0.61	0.21	0.30
Quantification limit (μg mL^{-1})	2	0.7	1
R.S.D. (%) (n = 10)	2.97[a]	4.31[b]	4.86[b]

[a] For a concentration level of 5 μg mL^{-1}.
[b] For a concentration level of 8 μg mL^{-1}.

Table 2
Interference study

Foreign species	Tolerance ($\mu g\,mL^{-1}$ interferent/$\mu g\,mL^{-1}$ analyte)		
	Salicylamide[a]	Caffeine[b]	Propyphenazone[c]
Saccharose, glucose, lactose	>20[d]	>20[d]	>20[d]
Manitol	7	7	7
Ascorbic acid	14	15	>20[d]
Phenylephrine	9	9	10
Acetylsalicylic acid	1	>20[d]	>20[d]
Paracetamol	1	>20[d]	>20[d]
Paracetamol[e]	>3[d]	>20[d]	>20[d]
Chlorphenamine maleate	>2[d]	>2[d]	>2[d]

[a] 10 $\mu g\,mL^{-1}$ of salicylamide.
[b] 8 $\mu g\,mL^{-1}$ of caffeine.
[c] 10 $\mu g\,mL^{-1}$ of propyphenazone.
[d] Maximum ratio tested.
[e] Measuring SLC at 315 nm.

quency was obtained with satisfactory sensitivity. It is important to notice that the sensitivity was less important than the sample frequency, as the concentration of the analytes in pharmaceutical preparations is high, but the main objective of this work was to focus on the development of a routine method of analysis, so the speed of the method is a critical aspect.

The flow-rate was investigated from 0.7 to 1.4 mL min^{-1}. By increasing it, both the analytical signal and the sample frequency increased. This is explained taking into account that an increase in the flow-rate means a higher volume of sample being introduced into the system in the same time, so the signal is increased. The sample frequency is also increased due to the high flow-rate. So the highest possible flow-rate, avoiding overpressures due to the solid phase placed in the precolumn and flow-through cell, was selected. 1.2 mL min^{-1} was the chosen value; higher flow rates resulted in overpressures in the flow network.

3.5. Figures of merit

Taking into account the optimized conditions, the analytical parameters of the system were studied. The R.S.D. ($n = 10$) were all under 5% for 5 $\mu g\,mL^{-1}$ of CF and 8 $\mu g\,mL^{-1}$ of SLC and PFZ. The detection limits and quantification limits were calculated following the 3σ and 10σ criteria. All the analytical parameters are detailed in Table 1.

3.6. Study of foreign species

In order to determine the effect of possible interferences, a tolerance study was carried out with those compounds that are usually found along with SLC, CF and PFZ in pharmaceuticals, both excipients and active principles.

The study was carried out with 10 $\mu g\,mL^{-1}$ of SLC and PFZ, and 8 $\mu g\,mL^{-1}$ of CF. Foreign species were added to the samples at interferent/analyte ratios higher than those usually found in pharmaceuticals.

A compound was considered to interfere if a variation of more than ±5% was observed in the analytical signal. If such a variation was observed, the foreign species concentration was diminished until an error less than ±5% was obtained.

The use of the C_{18} solid micro-beads (both in the precolumn and flow-cell) and the working conditions (pH of

Table 3
Applications to pharmaceuticals

Sample[a]	SLC			CF			PFZ		
	Nominal value (mg)	Found (mg)	R.S.D. (%)	Nominal value (mg)	Found (mg)	R.S.D. (%)	Nominal value (mg)	Found (mg)	R.S.D. (%)
Cafiaspirina	–	–	–	50	49.2	3.2	–	–	–
Tonopan	–	–	–	40	41.6	3.5	175	182.4	3
Tonopan semisynthetic[b]	50	45.6	1.8	40	42.4	3.2	175	184.6	2.8
Rinomicine activated	150	153	2.1	30	30	3	–	–	–
Yendol	500	540	4.8	30	29.8	1.8	–	–	–
Coricidin	190	199.1	1.9	30	31.1	1.8	–	–	–
Optalidón	–	–	–	25	25.5	2.7	175	183.8	2.2
Hubergrip	300	295.9	1.5	25	22.9	1	250	225	4

[a] Composition of samples—Cafiaspirina activated tablets (Bayer): acetylsalicylic acid, 500 mg; caffeine, 50 mg. Tonopan pellets (Novartis): dihydroergotamine mesilate, 0.5 mg; caffeine, 40 mg; propifenazone, 175 mg. Rinomicine activated tablets (Fardi): chlorpheniramine maleate, 4 mg; phenylephrine hydrochloride, 10 mg; salicylamide, 150 mg; paracetamol, 150 mg; caffeine, 30 mg. Yendol granular packets (Faes): paracetamol, 200 mg; salicylamide, 500 mg; chlorpheniramine maleate, 3 mg; caffeine, 30 mg. Coricidin capsules (Schering-Plough): chlorpheniramine maleate, 4 mg; salicylamide, 190 mg; caffeine, 30 mg; ascorbic acid, 50 mg. Optalidon pellets (Novartis): propifenazone, 175 mg; caffeine, 25 mg; saccharose, 89.87 mg. Hubergrip activated tablets (ICN Ibérica): salicylamide, 300 mg; propifenazone, 250 mg; caffeine, 25 mg; chlorpheniramine maleate, 2 mg.
[b] Tonopan semisynthetic was prepared by adding SLC to Tonopan.

Table 4
Recovery study in pharmaceuticals

Sample	SLC				CF				PFZ			
	Added (mg)	Found (mg)	R.S.D. (%)	Recovery (%)	Added (mg)	Found (mg)	R.S.D. (%)	Recovery (%)	Added (mg)	Found (mg)	R.S.D. (%)	Recovery (%)
Cafiaspirina	–	–	–	–	30	28	1.3	93.3	–	–	–	–
	–	–	–	–	100	105.1	1.8	105.1	–	–	–	–
	–	–	–	–	150	138.7	3.9	92.5	–	–	–	–
Tonopan	–	–	–	–	80	83.1	1.9	103.9	48	44.4	4.8	92.5
	–	–	–	–	160	145.9	2.4	91.2	120	124.2	2.1	103.5
	–	–	–	–	240	253	2.2	105.4	160	146.7	2.8	91.7
Tonopan semisynthetic	18.8	17.5	2.5	93.3	70	72.6	2.5	103.7	50	48.3	3.4	96.6
	43.8	46.2	3	105.7	150	142.1	2.8	94.7	140	145.8	2.8	104.1
	75	70	3.9	93.5	230	234.2	1.9	101.8	180	186.3	4.1	103.5
Rinomicine activated	30	31.5	3	105	45	45.2	1.9	100.4	–	–	–	–
	75	77	1.4	102.6	90	89	2.3	98.9	–	–	–	–
	225	205.5	3.7	91.3	150	156.6	2.8	104.4	–	–	–	–
Yendol	250	257.1	2.7	102.8	18	16.8	4	93.2	–	–	–	–
	500	539	4.8	107.8	30	27.4	5	91.5	–	–	–	–
	750	769.5	3.6	102.6	60	61.7	4.8	102.9	–	–	–	–
Coricidin	63.6	67.8	2.3	106.6	75	68.1	2,7	90.8	–	–	–	–
	127.1	118.2	3.1	93	125	127.5	3	102	–	–	–	–
	233	224.4	2.7	96.3	150	153.5	2	102.3	–	–	–	–
Optalidón	–	–	–	–	100	97.5	1.5	97.5	262.5	245	3.4	93.3
	–	–	–	–	125	133.8	1.9	107	700	691.2	4	98.8
	–	–	–	–	162.5	161.2	3.2	99.2	875	936.2	4.8	107
Hubergrip	116.7	108.3	1.8	92.9	75	70.9	3.3	94.5	166.7	150	3.8	90
	325	354.2	4	109	100	98.2	2.6	98.2	250	270.8	1.6	108.8
	533.4	566.7	2	106	125	133.1	4.4	106.5	375	412.5	2.5	108.9

the carrier, nature of eluting solution) allow the elimination of the interference of some compounds that usually come along with the target analytes due to the different kinetic of the retention–elution process in the solid support; other way the determination could not be possible due to the high interference.

The tolerance of potentially interfering compounds is much higher than the amount usually found in pharmaceuticals. Paracetamol was found to interfere in the determination of SLC, with a tolerated paracetamol/SLC ratio of only 1. Taking into account the absorbance spectra of both compounds, measuring SLC at 315 nm improved the tolerance ratio up to 3, so making possible the selective determination of SLC in the presence of paracetamol. The results obtained are detailed in Table 2.

3.7. Analytical applications

Following the previously described general procedure, the system was applied to the determination of the analytes in pharmaceutical preparations. Different pharmaceutical preparations of the Spanish Pharmacopoeia were used, such as capsules, activated tablets, pellets and granular packets. A pharmaceutical preparation containing all the three analytes was analyzed (the only available in the Spanish Pharmacopoeia) and several other pharmaceuticals containing binary mixtures were also determined. In addition, a semi synthetic pharmaceutical (containing all the analytes) was prepared by adding SLC to Tonopan (a pharmaceutical containing CF and PFZ). The results are shown in Table 3.

In addition, a recovery study was performed by adding three different amounts of one or several target analytes (depending on the pharmaceutical) to each tested preparation. The satisfactory results, detailed in Table 4, demonstrate the feasibility of the proposed methodology.

4. Conclusions

An interesting coupling of multicommutation and multioptosensing is here presented and demonstrated to be useful in the routine analysis of pharmaceuticals, being an alternative to chromatographic methods when only two or three analytes have to be simultaneously determined. In this work we have selected three active principles (SLC, CF and PFZ) that are widely used in the Spanish Pharmacopoeia, and this approach could be easily extended to the analysis of different target compounds by selecting appropriate conditions as nature and concentration of carrier and eluent solutions as well as the type of suitable solid support. As the impact of some usually used analytical methods on the environment is each time higher, the development of so-called environmentally friendly methodologies is the actual tendency of new ana-

lytical determinations. So multicommutation is an invaluable tool for the development of low-costly methods of analysis, with minimal reagents waste. The proposed methodology in this work is useful not only using UV photometric detection, but also with any kind of molecular detection technique, such as fluorescence or phosphorescence, obtaining higher sensitivity and selectivity, so increasing the range or applications.

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